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A.M.A. ARCHIVES OF

INTERNAL MEDICINE

Maintenance of Adrenal Cortical Responsiveness During Prolonged Corticoid Therapy
Irving I. Young, Vito De Filippis, Frank L. Meyer, and William Q. Wolfson

Treatment of Chronic Bronchitis and Bronchiectasis with Intravenous Tetracycline
Ronald E. Fox, Harry F. Dowling, George A. Saxton Jr., and Margaret Mellody

The Influence of the Endocrine Glands on Fatty Acid and Ketone Body Metabolism
Frank L. Engel

Emergency—Arsine Poisoning
W. J. McKinstry and J. M. Hickes

Metal-Fume Fever from Inhaling Zinc Oxide
Lloyd C. Rohrs

Subarachnoid Hematoma Complicating Ruptured Intracranial Arterial Aneurysm
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Metallic Mercury Embolization—Clinical and Experimental
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A. M. A.
ARCHIVES OF INTERNAL MEDICINE

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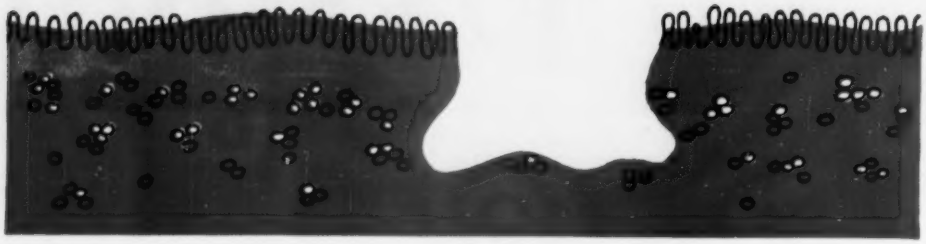

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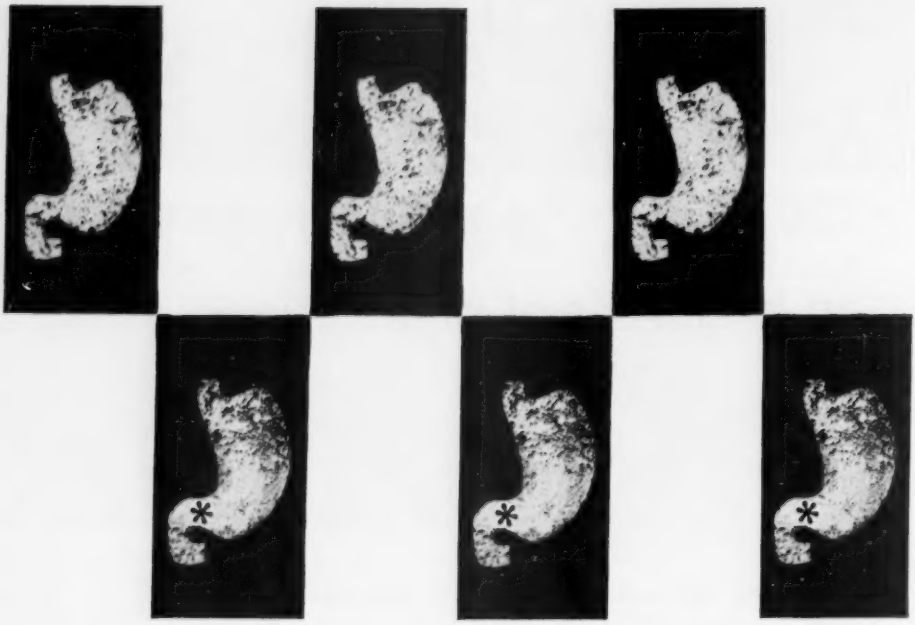

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A.M.A. ARCHIVES OF
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Maintenance of Adrenal Cortical Responsiveness During Prolonged Corticoid Therapy

Evaluation of Intermittent Administration of Repository Corticotropin Injection

IRVING I. YOUNG, M.D.; VITO De FILIPPIS, M.D.; FRANK L. MEYER, M.D., and WILLIAM Q. WOLFSON, M.D., Detroit

When given in adequate amounts, the therapeutically and metabolically active adrenal 17-hydroxycorticoids (17-OHCS) suppress the activity of the normal pituitary-adrenal axis. This is accomplished not by a direct action upon the adrenal cortex but by suppressing endogenous secretion of pituitary corticotropin (ACTH). This effect occurs to only a slight degree with a pure mineralocorticoid, such as desoxycorticosterone, but is marked with all of the adrenal corticoids used for systemic treatment, such as cortisone, hydrocortisone, prednisone, and prednisolone.

The first consequent of suppression of endogenous corticotropin secretion by exogenous corticoid is a marked diminution in the secretion of hydrocortisone, corticosterone, and adrenal androgens by the adrenal cortex; apparently diminution in aldosterone secretion is less pronounced. If adequate doses of exogenous steroid are given for long periods, the adrenal cortex slowly involutes and becomes atrophic. Accompanying this anatomic decrease in mass is a physiologic loss of sensitivity to stimulation, characterized by a decreasing output of corticoid in response to standard stimulating doses of corticotropin.

When the dose and period of administration have been sufficiently intense and prolonged, abrupt withdrawal of corticoid therapy, even in the absence of any added stress, usually results in a transient period of adrenal cortical hypofunction. Usually this lasts only several days to some weeks, but clinical observation suggests that without treatment it may sometimes persist for months. When they are subjected to significant added stress, patients from whom corticoids have been withdrawn after long-term administration may be precipitated into fully developed adrenal cortical insufficiency. This state may somewhat less easily and less commonly be produced after the immediate postwithdrawal period in some patients and during therapy in other patients if the stress is sufficient and additional corticoid is not given for protection. The most frequently reported cause of such adrenal cortical insufficiency has been the stress of surgery following the abrupt withdrawal of corticoid therapy. Such cases

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This study was supported in part by grants from the Michigan Chapter, Arthritis and Rheumatism Foundation, and The Armour Laboratories.

From the Department of Medicine, Wayne State University College of Medicine, and City of Detroit Receiving Hospital. Present address (Dr. Wolfson) 130 Waverly, Highland Park, Mich.

have appeared in the medical literature in small numbers since 1952,[1-6] and we know of other cases not reported.

During prolonged corticoid therapy, adrenal cortical responsiveness can be restored rather uniformly within two to five days by the administration of adequate amounts of exogenous corticotropin.[7] Since some evidence of adrenal cortical activity appears spontaneously approximately three or four days after corticoid withdrawal in experimental[8] and clinical[9] studies, it appears that inhibition of corticotropin production by high blood corticoid levels is usually rather transient. In the presence of stress, the limiting factor in hydrocortisone production may well be adrenal cortical atrophy rather than suppression of corticotropin.

If the view in the previous paragraph is correct, maintenance of some degree of adrenal cortical responsiveness during corticoid therapy should remove the defective responses to added stress and should prevent the appearance of symptoms of adrenal hypofunction after abrupt withdrawal of exogenous corticoid therapy. Various schedules of concurrent administration of corticotropin and corticoid have been examined for their ability to maintain adrenal responsiveness. Sporadic interruption of corticoid therapy for courses of corticotropin was suggested by early workers, but is unsatisfactory, since only two to four weeks of continuous suppressive therapy again induce significant unresponsiveness. Our early observations, summarized elsewhere,[10] suggested that if a sufficiently large dose of corticotropin was given once each week, adrenal responsiveness could usually, but not invariably, be maintained. Further study, reported here, confirms and amplifies this impression.

Materials and Methods

A group of 16 patients requiring prolonged corticoid therapy were selected for study. The indications for therapy included rheumatoid arthritis, disseminated lupus erythematosus, and bronchial asthma.

Prior to the institution of combined corticoid-corticotropin therapy, each subject was tested to establish the state of his adrenal cortical responsiveness. The majority were then given a combined program of hydrocortisone, cortisone, or prednisone for five or six days per week and high-potency repository corticotropin injection (corticotropin gel) in varying dosage on each seventh day. Two subjects were given corticoid therapy five days per week and repository corticotropin injection two days per week, on each third and seventh day.

If clinical response was satisfactory, the daily dose of steroid was adjusted to the patients' therapeutic requirements. If an incomplete response was obtained, dosage was increased to the maximum safely tolerated state of hypercorticism. The total weekly dose of corticotropin ranged from 100 to 320 units and varied with the state of the patients' adrenal cortical responsiveness.

Each subject was observed during a control period of corticoid therapy alone, either before or after a period of combined therapy, to substantiate the adrenal suppressive effect of approximately equivalent doses used during the periods of combined therapy. The importance of this precaution is emphasized by the fact that four other subjects observed during this period of study were not made unresponsive by prolonged administration of steroids in doses adequate to control symptoms of disease and to theoretically induce pituitary-adrenal suppression.

Two of these patients are of particular interest because both the basal pretreatment urinary excretion of 17-OHCS and the pretreatment rise in urinary 17-OHCS following a standardized 100 unit repository corticotropin injection test were supernormal. A normal degree of adrenal cortical responsiveness persisted after continuous administration of prednisone in doses of 15 mg. per day in one and 20 mg. per day in the other for a period of eight weeks. At no time did any of the group manifest any symptoms or signs of hypercorticism prior to the administration of exogenous steroids. Such failures to suppress pituitary-adrenal activity emphasize the fact that there may be considerable variability in the suppressive dose of exogenous steroid in apparently normal human subjects.

Evaluation of Adrenal Cortical Responsiveness and Basal Activity.—Basal adrenal cortical activity was estimated by the 24-hour urinary excretion of 17-OHCS. Adrenal cortical responsiveness was evaluated by the determination of the fall in peripheral blood eosinophils eight hours after a 100 unit intramuscular injection of purified corticotropin and by the increase in 17-OHCS excretion during the 24 hours immediately following this

dose of corticotropin.* The stimulating doses of repository corticotropin injection in these subjects under study thus periodically served as a test dose as well. When urine collections were made, all steroids were withdrawn for a 24-hour period prior to the initial collection, or the patient was given minimal doses of fludrocortisone. Steroid therapy was not resumed until a second 24-hour specimen was obtained after a stimulating dose of repository corticotropin injection. Completeness of urine collections was routinely checked by creatinine determinations.

The response to a 100 unit dose of human bioassayed reference corticotropin given intramuscularly has been found in this laboratory to be essentially equal to the response which others have reported following an eight-hour continuous intravenous infusion of 25 units of corticotropin. A complete discussion of the intramuscular technique has been given in a previous report.[10] Some investigators have reported a fairly high percentage of persons who do not respond adequately to reference corticotropin given intramuscularly but do respond to intravenous infusions. In our experience of between 1500 and 2000 such tests, we have found inadequate responses in only two types of situation: (1) when it could be shown that the human bioassay of the corticotropin was not equal to that reported by the manufacturer on the basis of animal assay and (2) when, after prolonged therapy with corticotropin, partial species-specific refractoriness to corticotropin given intramuscularly could be demonstrated in an occasional person. No person who has not previously received prolonged corticotropin treatment has failed to respond to reference corticotropin given intramuscularly, provided that the potency of the material was established by human bioassay to be equal to the 100 unit dose prescribed in the test. With this precaution, the 100 unit repository corticotropin injection test approximates the generally accepted 25 unit eight-hour intravenous corticotropin test.

Normal Responses.—Eight hours after a 100 unit intramuscular dose of repository corticotropin injection every normal subject shows a greater than 60% fall in blood eosinophil level, and the median fall is 100%. Ninety per cent of the subjects show a fall in blood eosinophils which exceeds ninety per cent. In this laboratory, 17-OHCS are estimated as butanol-extractable phenylhydrazine-reactive material, using a slight modification of the Reddy technique.[11] Normal basal excretion is 3.6 to 19.7 mg. per 24 hours, with a tendency for men to have somewhat higher outputs than women. In normal adults, the 24-hour output of 17-OHCS is from 5.5 to 34.4 mg. per 24 hours higher after 100 units of corticotropin than upon the preceding control day, with an average increase of 19.6 mg. per 24 hours.

Abnormal Responses.—An abnormal response to this standardized test may be of three types:

(*a*) Hyperresponsive: A 100 unit test dose elicits a significantly greater than normal response, as may be seen in subjects with Cushing's syndrome due to bilateral adrenal cortical hyperplasia.

(*b*) Hyporesponsive: Grade 1. Little or no response is noted to the 100 unit test dose, but a normal increase occurs with a single large dose, over 140 units.

(*c*) Hyporesponsive: Grade 2. No single dose of repository corticotropin injection will give a normal urinary corticoid increase, using 320 units as an arbitrary limit of dosage.

(1) Temporary and reversible with repeated dosage, as seen in most patients during prolonged corticoid therapy.

(2) Permanent. This phenomenon, characteristic of Addison's disease, has not been so far described following prolonged corticoid therapy, but has occurred after removal of an adrenal adenoma producing Cushing's syndrome.[10]

Results

An attempt has been made to answer the following questions: (*a*) Can a normal degree of adrenal cortical responsiveness be maintained by intermittent administration of repository corticotropin injection at weekly or biweekly intervals? (*b*) Can corticoid-induced adrenal cortical unresponsiveness be restored by intermittent administration of repository corticotropin injection?

A. Maintenance of Adrenal Cortical Responsiveness by Intermittent Administration of Repository Corticotropin Injection.—1. Effect of 100 Units of Repository Corticotropin Injection Weekly: Four patients with initially responsive adrenal cortices were given suppressive doses of steroids plus 100 units of repository corticotropin injection per week. Periods of therapy ranged from 6 to 22 weeks. Three of the four patients proved to be unresponsive to the standard 100 unit repository corticotropin injection test at the conclusion of the period of combined therapy, as measured by urinary 17-OHCS excretion. Patient 2 (Table 1)

* In this report, unless otherwise specified, corticotropin refers to a long-acting preparation of U. S. P. reference corticotropin, the high-potency type of the hormone.

TABLE 1.—*Summary of Data in Combined Corticotropin-Corticoid Therapy*

Patient	Functional Status of Adrenal Cortex Prior to Combined Therapy	Duration of Combined Therapy, Wk.	Steriod Used	Total Dose, Mg.	Average Daily Dose, Mg.	Week of Therapy	Repository Corticotropin Injection, Units	Urinary 17-OHCS, Mg. Rise/ 24 Hr.	8 Hr. Eosinopenia, % Fall	Adrenal Cortical Responsiveness at Conclusion of Therapy
					100 Units Repository Corticotropin Injection per Week					
1	Responsive	22	Hydrocortisone;	5,390	70.0	22	100	1.5	--	Not maintained
			cortisone	5,775	75.0					
2	Responsive	22	Hydrocortisone;	5,300	55.2	19	100	0.0	--	
			cortisone	3,450	95.8	22	200	0.0	--	Not maintained
3	Responsive	6	Hydrocortisone	2,270	54.0	6	100	0.0	22	Not maintained
4	Responsive	6	Cortisone	2,100	50.0	6	100	--	0	Demonstrable but subnormal
						4	150	16.7	--	
					200 to 320 Units Repository Corticotropin Injection per Week					
5	Unresponsive (corticoid-induced)	6	Hydrocortisone	2,070	49.5	6	200	0.0	--	Not restored
6	Unresponsive	11	Cortisone	3,500	45.5	10	200	11.2	--	Demonstrable but subnormal
						11	100	0.0	--	
7	Unresponsive	8	Cortisone	2,825	50.4	7	200	13.4	--	Demonstrable but subnormal
						8	100	1.0	--	
1	Unresponsive	8	Hydrocortisone	2,400	50.0	8	200	9.9	--	Demonstrable but subnormal
						9	100	0.0	--	
8	Unresponsive	12	Hydrocortisone	3,820	53.0	12	200	1.3	--	Not restored
9	Responsive	4	Prednisone	645	23.0	4	200	--	0	Not maintained
10	Responsive	25	Cortisone	5,390	36.0	5	200	--	79	
						12	200	38.5	--	
						14	100	5.8	--	Maintained
						25	10 I.V.	4.6	--	
4	Responsive	14	Cortisone	4,750	47.6	9	200	9.0	--	
						12	200	20.3	--	
						14	100	3.0	--	Demonstrable but subnormal
						15	100	18.6	--	
11	Responsive	9	Prednisone	945	15.0	5	100	10.4	--	
						9	100	5.0	--	Maintained
12	Responsive	11	Cortisone;	3,220	66.0	9	320	11.9	--	
			hydrocortisone	1,140	40.6	11	100	9.3	--	Maintained
					100 Units Repository Corticotropin Injection Twice Weekly					
13	Responsive	19	Prednisone	2,800	21.0	5	100	15.7	--	Maintained
						19	100	5.6	--	
14	Responsive	6	Cortisone	2,240	53.3	4	100	--	80	
						6	100	--	80	Maintained

had some months previously developed acute adrenal cortical insufficiency in the face of stress while given corticoid therapy alone. Adrenal cortical responsiveness was subsequently restored, but after 19 weeks of combined therapy 100 units of repository corticotropin injection caused no rise in urinary 17-OHCS excretion, and two weeks later a similar test with 200 units again failed to detect significant adrenal cortical responsiveness. Subsequently, administration of respository corticotropin injection, 100 units daily for three days, resulted in a satisfactory response, eliminating intramuscular inactivation of corticotropin as a likely explanation for the previous unresponsiveness.

Patient 4 responded satisfactorily to 150 units of repository corticotropin injection four weeks after combined therapy was started, but at six weeks a standard test with 100 units failed to produce a drop in total eosinophil count after eight hours, and the patient had no demonstrable subjective or objective clinical response. This represents an instance of quantitative hyporesponsiveness of the adrenal cortex, as discussed above.

2. Effect of 200 to 320 Units of Repository Corticotropin Injection Weekly: In five subjects an attempt was made to maintain adrenal responsiveness by weekly administration of 200 units of repository corticotropin injection. All initially had responsive adrenal cortices.

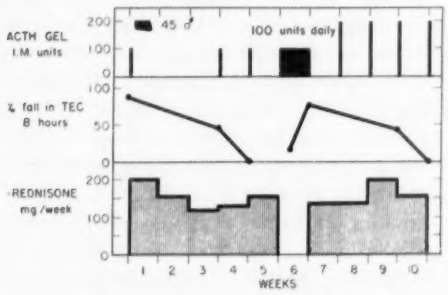

Fig. 1 (Patient 9).—Failure to maintain adrenal cortical responsiveness by intermittant administration of 200 units of repository corticotropin injection per week.

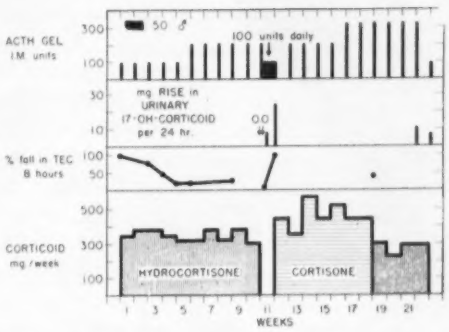

Fig. 2 (Patient 12).—Adrenal cortical responsiveness suppressed despite 100 units repository corticotropin injection per week but maintained by 200-320 units per week.

Patient 9 (Fig. 1) had been given repository corticotropin injection for many months prior to the administration of prednisone. Within four weeks, an average dose of 23 mg. per day resulted in suppression of adrenal cortical activity, as measured by his clinical and eosinopenic response to corticotropin. This was promptly restored by 100 units of repository corticotropin injection daily for five days, but could not be maintained subsequently by 200 units per week.

Three patients were maintained in a responsive state, and one exhibited a Grade 1 hyporesponsiveness after 14 weeks of combined therapy.

Figure 2 illustrates the course of Patient 12 while maintained on varying doses of repository corticotropin injection. The average daily suppressive dose of exogenous corticoid remained fairly constant during the entire period of observation. One hundred units of repository corticotropin injection proved insufficient to maintain adrenal responsiveness during five weeks of combined therapy, and this could not be restored by 200 units per week for six weeks. Following restoration of responsiveness by daily administration of 100 units of repository corticotropin injection for seven days, 200 units per week was begun. The patient's symptomatic response to this dose of corticotropin was satisfactory, but the eosinopenic response gradually de-

TABLE 2.—*Maintenance of Adrenal Cortical Responsiveness After a Period of Combined Therapy*

Therapy	Normal	Hyporesponsive	
		Grade 1	Grade 2
Corticoids alone	0	0	11
Corticoids plus 100 units repository corticotropin injection weekly	0	1	3
Corticoids plus 200-320 units repository corticotropin injection weekly	3	1	1
Corticoids plus 100 units repository corticotropin injection twice weekly	2	0	0

creased. On the fifth week, 320 units per week was instituted, and after eleven weeks a normal response to 100 units of repository corticotropin injection was demonstrated.

3. Effect of 100 Units of Repository Corticotropin Injection Twice Weekly: Two patients were given 100 units of repository corticotropin injection every three to five days while on corticoid therapy. As noted in Table 2, responsiveness was maintained in both.

Large doses of repository corticotropin injection, given at weekly or biweekly intervals, therefore appear to be necessary to maintain adrenal cortical responsiveness in the majority of subjects on prolonged corticoid therapy. These data are summarized in Table 2.

B. Restoration of Adrenal Cortical Responsiveness by Intermittent Administration of Repository Corticotropin Injection.—Five trials of therapy were followed for from 6 to 12 weeks, during which time an attempt was made to restore responsiveness to adrenal cortices previously suppressed by corticoid therapy. In two subjects this goal was not achieved, as evidenced by a failure of urinary 17-OHCS to rise in response to as much as 200 units of repository corticotropin injection. In both of these patients normal responsiveness was subsequently produced by daily administration of 100 units of repository corticotropin injection for three days. Three subjects responded in a manner which is believed to indicate the presence of partial, but subnormal, adrenal cortical activity (Grade 1). All failed to show a significant rise in urinary 17-OHCS when given 100 units of repository corticotropin injection, but responded adequately to 200 units given on the preceding week. Again, a normal degree of responsiveness was readily restored by the administration of 100 units of repository corticotropin injection daily for three days.

Comment

Suppression of adrenal cortical activity by exogenous 17-OHCS has been confirmed by a number of experimental and clinical studies. Atrophy of the adrenal cortex, the morphological expression of depressed secretory activity, was described by Ingle [14] and subsequently by others in the experimental animal. Such atrophy is confined to the zona fasciculata and reticularis and does not involve the zona glomerulosa.[8]

Adrenal cortical atrophy has also been described in human autopsy studies. Sallasa et al.[1] have noted significant decreases in adrenal weight and depletion of the lipid content of cortical cells after administration of as little as 450 mg. of cortisone over a period of five days. Suppression of endogenous adrenal cortical secretion by 9-α halogenated steroids, prednisone, prednisolone, and hydrocortisone has also been demonstrated by decreases in urinary 17-ketosteroids and 17-OHCS excretion following their abrupt withdrawal in normal subjects and patients with adrenal hyperplasia.[15-16]

It is well established that the adrenal cortical suppressive effect of high blood corticoid levels is not mediated directly, but rather through suppression of the anterior pituitary production of corticotropin.[17] Morphological evidence reflecting this phenomenon, consisting of Crookes changes in the pituitary basophils, is rather uniformly seen.

Under normal circumstances the pituitary adrenal axis appears to be very sensitive to exogenous steroid. Hydrocortisone given intravenously has been observed to block corticotropin release in the stressed adrenalectomized rat within one to two

minutes.[18] Rukes et al.[2] have noted that 100 mg. of hydrocortisone, given intravenously over an eight-hour period, will produce transient suppression of adrenal cortical activity, as measured by urinary steroid excretion, most evident during the third eight-hour period after discontinuation of the infusion.

When suppressive corticoid therapy is continued for prolonged periods of time, the histological evidence of adrenal cortical atrophy is accompanied by a readily demonstrable unresponsiveness to exogenous corticotropin. Abrupt steroid withdrawal is then followed by a delayed recovery of the pituitary-adrenal axis. After prolonged suppressive therapy, histological evidence of recovery in the rat is usually observed to begin by the fourth day, is well advanced within 10 days, and is unquestionably complete by 45 days.[8] Parallel observations have been made in human studies, including observations on corticoid excretion following abrupt withdrawal of exogenous steroid.

Three patients studied by Calkins et al. developed symptoms and metabolic changes suggestive of adrenal insufficiency and diminished steroid excretion for three days. By the fourth day evidence of endogenous corticoid production was evident.[9] Forsham et al. have observed suppression of adrenal cortical responsiveness for periods up to 10 days after corticoid withdrawal, as determined by urinary 17-ketosteroid excretion.[19]

To date there have been no reported studies of urinary steroid excretion with or without corticotropin stimulation to indicate that adrenal cortical unresponsiveness can persist for prolonged periods of time after steroid withdrawal, but presumed cases of fatal stress-induced acute adrenal cortical insufficiency have been reported as long as four and one-half months after steroid withdrawal,[1] several with autopsy studies indicating that the adrenal cortex was still atrophic.

These unusual cases have not been satisfactorily explained. Without known exception, the corticoid-suppressed adrenal cortex can be restored to normal responsiveness by three to five days of maximum stimulation with exogenous corticotropin. Persistent adrenal cortical atrophy may conceivably be due to a permanent unresponsiveness, such as may occur following prolonged suppression of thyroid function due to TSH lack, or may imply that persistent anterior pituitary suppression exists. The possibility that hypopituitarism with respect to corticotropin existed prior to corticoid therapy must also be considered.

The majority of reported cases of corticoid-induced adrenal cortical insufficiency have followed the stress of surgery shortly after withdrawal of exogenous steroid. The following case illustrates the occurrence of acute adrenal cortical insufficiency while given hydrocortisone therapy. It is presumed that the stress of an acute infection in a patient with acute disseminated lupus erythematosus increased the requirement for steroid beyond that supplied and that the unresponsive pituitary adrenal axis was unable to elaborate hydrocortisone to meet this deficit.

CASE 8.—A 36-year-old Negro woman with disseminated lupus erythematosus had been given oral hydrocortisone therapy 39 days prior to hospitalization, on March 13, 1955. During this period of time she had taken an average of 104 mg. per day, or a total of 4065 mg.

She was hospitalized following an acute illness, characterized by chills, fever, cough, and chest pain. On admission she was very toxic, confused, and had a temperature of 105.2 F. She was in shock, with a blood pressure of 70/40 and a pulse rate of 120 per minute. There was a small pulmonary infiltrate in the left lower lobe, and sputum cultures subsequently revealed a pneumococcus.

In spite of the fact that oral hydrocortisone therapy was at no time discontinued and that 175 mg. of cortisone was given intramuscularly during the first 24 hours, she remained in shock. Large doses of penicillin and intravenous fluids were promptly administered. On the second hospital day, the possibility of hydrocortisone-induced adrenal insufficiency was seriously considered, and intravenous administration of hydrocortisone was begun (Fig. 3). Her blood pressure promptly rose to normal, and fever and toxemia disappeared.

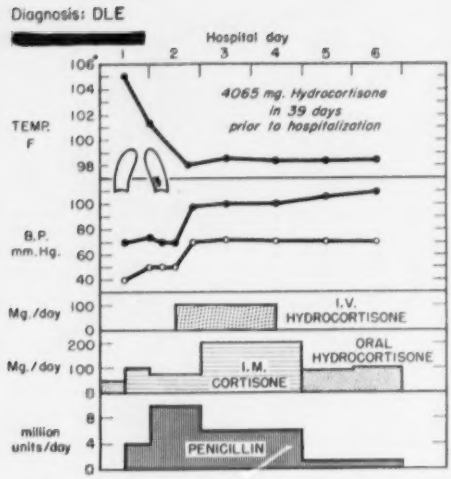

Fig. 3.—Corticoid-induced acute adrenal cortical insufficiency.

Adrenal cortical unresponsiveness was demonstrated a short time later by the failure of urinary 17-OHCS to rise following a test dose of 100 units of repository corticotropin injection (0.6 mg. per 24 hours). Responsiveness was readily restored by daily administration of 100 units of corticotropin for five days.

The present study was undertaken to explore the practicality of combining corticotropin with corticoid therapy to prevent adrenal cortical atrophy and unresponsiveness. Concurrent daily administration of corticotropin has been shown to be effective in dogs receiving cortisone and hydrocortisone.[20] In human subjects, intermittent injections of repository corticotropin injection at weekly intervals does not effectively maintain adrenal cortical responsiveness unless large individual doses are used. A total of 100 units per week did not prevent the development of absolute hyporesponsiveness in three of four subjects and was only partially effective in the fourth; 200 to 320 units per week was definitely more effective in that three of five subjects maintained a normal degree of responsiveness, and one had a demonstrable, but subnormal, responsiveness.

It appears that adequate doses of repository corticotropin injection (200 to 320 units per week) will usually prevent the development of a temporary absolute hyporesponsiveness, and thus the average adrenal responsiveness of patients given concurrent therapy will be higher than on corticoid therapy alone.

The restoration of adrenal responsiveness by exogenous corticotropin does not necessarily imply that the patient will be protected from stress, since by raising blood corticoid levels corticotropin itself causes suppression of endogenous corticotropin production. This is associated with histological evidence of Crookes changes in the basophils of the anterior pituitary. Furthermore, abrupt withdrawal of corticotropin after a prolonged period of therapy may be followed by a transient decrease in urinary excretion of 17-OHCS. It should be emphasized, however, that the functional status of the anterior pituitary does not necessarily correlate with the histological findings of degranulation, vacuolation, and hyalinization of the pituitary basophils.[21] Such changes appear to persist for weeks after withdrawal of corticotropin,[22] although indirect evidence of restored corticotropin secretion is usually evident within a matter of days.[23] Functional regression of pituitary adrenal activity may not be detectable at all after corticotropin withdrawal.[19]

In support of these observations, an unequivocal case of acute adrenal cortical insufficiency has to date not been reported following abrupt withdrawal of corticotropin or during stress in a corticotropin-treated patient. It may be that even small amounts of corticotropin elaborated by a partially suppressed gland may be sufficient to stimulate adequate production of hydrocortisone from a hyperplastic hyperresponsive adrenal cortex to meet stressful situations. Recent studies in the dog suggest that as little as 3% of the pituitary will provide sufficient corticotropin to maintain the adrenal cortical response to stress.[24]

Since patients given corticotropin therapy appear to be less vulnerable to stress-induced acute adrenal cortical insufficiency because of a responsive adrenal cortex, it

would follow that any attempt to maintain adrenal cortical responsiveness during prolonged corticoid therapy would be of value.

From a practical viewpoint, we do not yet know what degree of adrenal responsiveness is necessary for protection from stress-induced adrenal insufficiency and from post-corticoid-withdrawal symptoms. The efficacy of this program must be evaluated by further clinical observation of such patients during stress and following abrupt withdrawal of steroid therapy.

Summary

Adrenal cortical atrophy and unresponsiveness are commonly observed during and shortly after prolonged administration of adrenal cortical steroids. This state is reversible but when present renders the subject vulnerable to stress-induced acute adrenal cortical insufficiency.

Concurrent administration of repository corticotropin injection at weekly intervals will usually prevent the development of such unresponsiveness if individual doses of 200 units or more are used.

Adrenal cortical unresponsiveness cannot be restored by the intermittent administration of large weekly doses of corticotropin during prolonged corticoid therapy.

Combined corticotropin-corticoid therapy may be of value in preventing the development of stress-induced acute adrenal cortical insufficiency.

Wayne State University College of Medicine, Department of Medicine (7).

REFERENCES

1. Salassa, R. M.; Bennett, W. A.; Kealing, F. R., Jr., and Sprague, R. G.: Postoperative Adrenal Cortical Insufficiency: Occurrence in Patients Previously Treated with Cortisone, J. A. M. A. 152:1509, 1953.

2. Rukes, J. M.; Orr, R. H.; Forsham, P. H., and Galante, M.: The Use of Intravenous Hydrocortisone in Major Surgery, Ann. New York Acad. Sc. 61:448, 1955.

3. Lewis, L.; Robinson, R. F.; Yee, S.; Hacker, L. A., and Elsen, G.: Fatal Adrenal Cortical Insufficiency Precipitated by Surgery During Prolonged Continuous Cortisone Treatment, Ann. Int. Med. 39:116, 1953.

4. Fraser, C. G.; Preuss, F. S., and Bigford, W. D.: Adrenal Atrophy and Irreversible Shock Associated with Cortisone Therapy, J. A. M. A. 149:1542, 1952.

5. Keitzer, W. A., and Cheek, P. E.: Acute Adrenal Insufficiency, A. M. A. Arch. Int. Med. 94:326, 1954.

6. Kittredge, W. E.: Potential Hazards of Cortisone in Treatment of Prostatic Cancer: Report of a Fatal Case, Tr. Am. A. Genito-Urin. Surgeons 46:57, 1954.

7. Fredell, E. W.; Johnson, H. P.; Krupp, M. A.; Engleman, E. P., and McGrath, A. K.: Adrenocortical Function During Long-Term Cortisone Therapy, A. M. A. Arch. Int. Med. 95:411, 1955.

8. Winter, C. A.; Silber, R. H., and Stoerk, H. C.: Production of Reversible Hyperadrenocortinism in Rats by Prolonged Administration of Cortisone, Endocrinology 47:60, 1950.

9. Calkins, E.; Bauer, W.; Engel, L. L., and Carter, P.: Metabolic and Endocrinologic Consequences of Abrupt Cessation of Long-Term Cortisone Therapy in Rheumatoid Arthritis, J. Clin. Endocrinol. 15:856, 1955.

10. Young, I. I.; De Filippis, V.; Meyer, F. L., and Wolfson, W. Q.: The Effect of Intermittent Administration of ACTH on the Adrenal Cortical Responsiveness of Patients on Prolonged Corticoid Therapy, Clin. Res. Proc. 3:201, 1955.

11. Jenkins, D.; Forsham, P. H.; Laidlaw, J. C.; Reddy, W. J., and Thorn, G. W.: Use of ACTH in the Diagnosis of Adrenal Cortical Insufficiency, Am. J. Med. 18:3, 1955.

12. Wolfson, W. Q.: The 3 Subtypes of Pituitary Adrenocorticotropin: Basic Physiology, Quantitative Human Pharmacology, and Medical Usefulness of ACTH-Corticotropin ("Corticotropin, Crude," "U. S. P. Corticotropin," ACTX-Corticotropin ("Corticotropin, Purified," "Corticotropin A," "Type I Purified ACTH") and ACTIDE-Corticotropin ("Corticotropin B"), A. M. A. Int. Med. 92:108, 1953.

13. Margen, S.: Personal communication to the authors.

14. Ingle, D. J., and Kendall, E. C.: Atrophy of the Adrenal Cortex of the Rat Produced by the Administration of Large Amounts of Cortin, Science 86:245, 1937.

15. Goldfein, A.; Saint-Marc, J.; Beigelman, P. M., and Ganong, W. F.: The Suppression of Endogenous Adrenaocortical Secretion with 9-Alpha-Fluorohydrocortisone, J. Clin. Endocrinol. 15:850, 1955.

16. Kupperman, H. S.; Blatt, M. H. G., and Wiesbader, H.: Comparative Effect of Metacortandracin, 9-α-Fluorohydrocortisone, and Hydro-

cortisone upon ACTH Secretion in Man, J. Clin. Endocrinol. 15:850, 1955.

17. Lewis, R. A.; Rosemberg, E., and Wilkins, L.: The Effects of 17-Hydroxy-11-Dehydrocorticosterone upon the Adrenals of Normal and of Hypophysectomized Rats Maintained with Adrenocorticotropin, Endocrinology 47:414, 1950.

18. Sydnor, K. L.: Blood ACTH in the Stressed Adrenalectomized Rat After Intravenous Injection of Hydrocortisone, Endocrinology 56:204, 1955.

19. Forsham, P. H.; Thorn, G. W.; Frawley, T. F., and Wilson, L. W.: Studies on the Functional State of the Adrenal Cortex During and Following ACTH and Cortisone Therapy, J. Clin. Invest. 29:812, 1950.

20. Collins, E. J., and Olsen, K. J.: Inhibition of Steroid-Induced Adrenal Hypofunction, Proc. Soc. Exper. Biol. & Med. 87:76, 1954.

21. Golden, A., and Bondy, P. K.: Cytologic Changes in Rat Adenohypophysis Following Administration of Adrenocorticotrophin or Cortisone, Proc. Soc. Exper. Biol. & Med. 79:252, 1952.

22. Landing, B. H., and Feriozi, D.: Effects of ACTH and Cortisone on the Adrenals and Pituitaries of Children with Acute Leukemia, J. Clin. Endocrinol. 14:910, 1954.

23. Ely, R. S.; Ainger, L. E.; Seely, J. R.; Done, A. K., and Kelly, V. C.: Studies of 17-Hydroxycorticosteroids: X. Urinary Excretion of 17-Hydroxycorticosteroids in Patients with Rheumatic Fever, J. Clin. Endocrinol. 15:523, 1955.

24. Ganong, W. F., and Hume, D. M.: The Effect of Graded Hypophysectomy on Thyroid, Gonadal, and Adrenocortical Function in the Dog, Endocrinology 59:293, 1956.

Treatment of Chronic Bronchitis and Bronchiectasis with Intravenous Tetracycline

Results, as Judged by Studies of the Sputum and Tests of Pulmonary Function

RONALD E. FOX, M.D.; HARRY F. DOWLING, M.D.; GEORGE A. SAXTON Jr., M.D., and MARGARET MELLODY, M.S., Chicago

Antibiotics have been successful in controlling many of the cases of pneumonia that occur in patients with chronic bronchitis or bronchiectasis, but their effect upon the underlying disease is uncertain. Analysis of the problem is complicated by uncertainty as to which of the many micro-organisms that are cultured from the sputum of patients with bronchiectasis are etiologic and which are merely saprophytes. Mulder and his associates [1-3] and many other investigators [4-8] stressed the importance of Hemophilus influenzae in chronic bronchitis and bronchiectasis. Pneumococci appear to be the next most frequent pathogenic organisms, although the frequency with which they are cultured depends upon the thoroughness of the search. Stuart-Harris et al.[7] cultivated them from 58% of sputa from patients with bronchiectasis and 51% of sputa from patients with chronic bronchitis. Allison and his associates [4] found them in only 11% of their patients with bronchiectasis. May [8] cultured them from 63% of purulent sputa and 46% of mucoid sputa from patients with chronic bronchitis. Brown and his co-workers [9] found pneumococci in 74% of 83 specimens from patients with chronic bronchitis and emphysema. Other bacteria that are considered to be pathogenic are Micrococcus pyogenes var. aureus, Klebsiella pneumoniae, and the β-hemolytic Streptococcus.[4]

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From the Research and Educational Hospitals, University of Illinois, and the Departments of Medicine and Preventive Medicine, University of Illinois College of Medicine.

The reasons why these five organisms are considered to be pathogenic are that (1) they frequently cause acute pulmonary infections; (2) in bronchiectasis and chronic bronchitis one or more of these organisms are present when the sputum is purulent, whereas they are found less often in mucoid, nonpurulent sputum [2,10]; (3) these organisms usually disappear from the sputum after therapy with antibiotics that cause improvement [2,5,10,11]; (4) Hers and Mulder [3] saw H. influenzae between the epithelial cells and in the submocosa of a bronchiole of a lung removed from a patient with bronchiectasis and H. influenzae and pneumococci in the epithelium and submucosa of the bronchi and bronchioles of a lung of another patient.

Antibiotic therapy has been directed at the organisms that are considered to be pathogenic in bronchiectasis and chronic bronchitis. Since pneumococci and Group A streptococci are inhibited by a number of antibiotics, since most staphylococci are sensitive to one of several antibiotics, and since Klebsiella is not often cultured, H. influenzae presents the biggest problem. Mulder and his associates [2] used penicillin, streptomycin, chloramphenicol, and, in a few cases, the tetracycline analogues. The best results were obtained with large doses of penicillin combined with streptomycin. Knox, Elmes, and Fletcher [11] were unable to suppress H. influenzae infections or to eliminate exacerbations of chronic bronchitis with combined penicillin-streptomycin aerosol therapy.

Barach and his co-workers [12] reported that 58 of 70 patients with bronchiectasis improved markedly or moderately on treatment with systemic penicillin, 15 of 18 treated with oral chlortetracycline or oxytetracycline, and 11 of 13 treated with chloramphenicol. May [10] found penicillin to be the most effective antibiotic in pneumococcic infections and chloramphenicol in H. influenzae infections. Streptomycin or chlortetracycline in doses of 2 gm. a day was successful in ridding the sputum of H. influenzae in some cases but not in others. Franklin and Garrod [5] treated 36 patients with bronchiectasis with chloramphenicol. Doses of 20 mg. per kilogram three times a day consistently diminished the amount of sputum and eliminated the "pathogenic" bacteria. They discontinued this method of therapy, however, when one patient died of aplastic anemia. Allibone et al.[6] observed the disappearance of H. influenzae from the sputa of all of the bronchiectatic children who were treated with sulfonamides and oxytetracycline or erythromycin, but not consistently from the sputa of those who received antibiotics alone.

In spite of the fact that the tetracyclines inhibit H. influenzae in vitro, it is obvious that none of the antibiotics has been consistently effective in removing "pathogens" from the sputum and rendering the sputum nonpurulent in these diseases. Chloramphenicol has perhaps given the best results, but the possibility of blood dyscrasia makes it unsuitable. While the tetracyclines often produce a satisfactory result when used in full oral doses, they may at other times have no effect upon the course of the disease. It occurred to us that higher doses might be more effective. Since gastrointestinal symptoms usually prevent higher oral doses we decided to hospitalize the patients and give tetracycline intravenously. Although defects in pulmonary function have been described in a few cases of bronchiectasis,[13] no comparisons of function before and after antibiotic therapy have been made, nor has any correlation of pulmonary function with sputum volume or bacteriology been attempted. This paper is a report of 10 patients with bronchiectasis and 5 with chronic bronchitis who were treated with intravenous tetracycline, whose sputa were carefully studied, and on whom pulmonary function tests were performed.

Methods

The criteria used for inclusion of a patient in this series included a history of chronic productive cough. A bronchogram was obtained on every patient, and bronchoscopy was performed unless contraindicated. There was no selection of patients except that they should be ambulatory, they should not be suffering from an acute exacerbation of the disease, and they should not have any complicating pulmonary disease or abnormality except emphysema. None of the patients had received antibiotics during the four weeks prior to hospitalization, except one who had received small doses of penicillin until the fifth day before tetracycline therapy (Patient 7).

Pulmonary ventilation studies consisted of vital capacity, timed vital capacity, and maximal breathing capacity. These were carried out before and after tetracycline therapy. In some patients, arterial blood gas tensions and nitrogen washout curves were also determined. In the three patients who were first given a course of intravenous dextrose solution, the tests were done before and after the control period and after the course of tetracycline.

The total and the timed vital capacities were measured on the Collins Vitalometer of Gaensler, with the patient in the standing position. The maximum breathing capacities were measured with a low-resistance Rudolph valve, the expired air being collected in a Douglas bag over a period of 20 seconds. The collected volume was measured in a Tissot spirometer and corrected for temperature and barometric pressure to standard conditions. An average of three determinations was taken as the reading of total and timed vital capacities on each occasion, but the maximum breathing capacity was measured only once on each occasion of study. In most cases, the three ventilatory measurements were repeated on three different days before and again after treatment in order to minimize the effect of training and fatigue from repeated testing.

Sputum volume was measured for each 24-hour period during hospitalization. One or more specimens of sputum were cultured soon after admission and during and after tetracycline therapy. These specimens, after they were stained with Gram's stain, were observed for purulence macroscopically

and microscopically. Sputa were cultured aerobically on human blood trypicase-soy agar plates, Levinthal agar plates, and chocolate agar plates after having first been liquefied with pancreatin according to the method of Rawlings.[14] Colonies that appeared to be staphylococci, pneumococci, hemolytic streptococci, or H. influenzae were picked for isolation to Levinthal broth, human blood trypicase soy broth, and tryptose phosphate broth. They were then identified in the usual manner.

Tetracycline was given in doses of 0.5 gm. at 8- to 12-hour intervals for five days. The two younger patients were given an equivalent dose on the basis of body weight. In certain cases, where sputum volume did not diminish promptly, the dose was increased to 0.5 gm. at six-hour intervals for five days.

Three patients were given a 5% solution of dextrose in purified water, U. S. P., by continuous intravenous infusion for five days preceding the tetracycline therapy, so that observations could be made before and after each type of intravenous infusion and the effect of bed rest and symptomatic therapy could be determined.

Results

As shown in Table 1, the presumed pathogenic organisms disappeared in every instance. M. pyogenes var. aureus was found in the sputum of Patients 1 and 4 after treatment. The sputum of Patient 1 was still purulent after therapy; the sputum of Patient 4 was clear. Proteus appeared in the sputum of Patients 13 and 14 after therapy, although the sputum was not purulent.

The average daily volume of the sputum was reduced to between 44% and 97% of the original volume in 14 of the 15 cases. Patient 10, who showed no reduction after therapy, had green mucoid sputum before therapy from which a β-hemolytic Streptococcus was cultured. The average sputum volume of this patient before and after tetracycline therapy was the same, but after tetracycline it became watery and colorless. The patient stated that this was merely saliva, and this opinion is substantiated by the fact that he did not produce any sputum after leaving the hospital and was symptom-free on the last follow-up, five months after therapy.

The average decrease in sputum for all of the 15 patients was 41 cc., or 62% of the original volume. The decrease in the volume of sputum in the patients whose sputa contained pathogens was no greater than the decrease in the patients whose sputa contained no pathogens. The decrease in sputum of the two patients whose sputa contained M. pyogenes after therapy was

TABLE 1.—*Symptoms, Temperature, and Sputum Findings in Patients Treated with Tetracycline*

Patient	Race	Sex	Age	Duration of Symptoms, Yr.	Pathogens in Sputum		Daily Average Sputum Volume, Cc.				Temperature During 5 Days, F	
					Before Therapy	After Therapy	3 Days Before Therapy	3 Days After Therapy	Decrease No.	Decrease Per Cent	Before Therapy	After Therapy
					Patients with Bronchiectasis							
1	W	F	47	3	D. pneumoniae	M. pyogenes var. aureus	183	92	91	50	None	None
2	W	F	18	16	H. influenzae	None	11	4	7	64	None	0.2
3	W	F	28	28	None	None	32	12	20	63	None	0.2
4	W	F	42	1½	H. influenzae	M. pyogenes var. aureus	97	50 *	47	49	0.2	None
5	W	F	34	15	H. influenzae	None	50	7	43	86	0.4	None
6	W	M	69	7	D. pneumoniae	None	70	3	67	96	2.0	None
7	W	F	29	28	H. influenzae D. pneumoniae	None	58	22	36	62	None	None
8	W	M	15	13	H. influenzae	None	33	1	32	97	1.0	None
9	W	M	19	17	H. influenzae	None	53	2	51	96	None	None
10	N	M	59	5	β-Streptococcus	None	18	18	0	0	1.2	0.4
					Patients with Chronic Bronchitis							
11	W	M	54	10	H. influenzae	None	113	58	55	51	0.2	None
12	W	F	55	16	None	None	17	2	15	88	0.4	None
13	W	M	54	Unknown	H. influenzae	None	40	20	20	50	0.2	None
14	W	M	48	11	None	None	150	52	98	65	None	None
15	W	M	59	31	H. influenzae M. pyogenes var. aureus	None	62	35	27	44	None	None

* One day only.

slightly less than the average decrease (50% and 49%, respectively).

Since these patients were not treated during an acute exacerbation of the disease, very little fever was present before therapy. Eight of the patients had slight rises in temperature during the three days before tetracycline therapy, ranging from 0.2 to 2 F (above a base line of 100 F by rectum). After therapy three patients had slight fever during the next three days, the highest temperature being 0.4 degree Fahrenheit. This was considered to be caused by the thrombophlebitis resulting from the irritative action of the tetracycline. Some degree of thrombophlebitis occurred in all of the patients as a result of the intravenous tetracycline. In only one patient was this sufficiently severe to require discontinuation of the tetracycline therapy after seven days. In all of the patients, the thrombophlebitis healed promptly after the tetracycline infusions were stopped, and there were no sequelae.

H. influenzae was found in the sputa of nine patients, in one case with a pneumococcus and in another case with M. pyogenes var. aureus. Pneumococci were found in sputa of two additional patients, and β-streptococci in the sputum of one. The sputa of three patients did not contain any of the so-called pathogens.

Table 2 shows the measurements of pulmonary ventilation before and after treatment with tetracycline. In those patients who received dextrose infusions also, these tests were done before and after the control period and after tetracycline therapy. Tests for pulmonary ventilation were not done on Patient 6.

The total vital capacity increased in nine patients, decreased in four, and remained the same in one. All of the decreases were less than 10% of the original value, while the increases in six patients were higher than 10% of the original value. In three cases in which intravenous dextrose was given as a control the amount of change was negligible, both after dextrose and after tetracycline.

The results with the one-second vital capacity test were essentially the same. Ten patients showed an increase after therapy, and in eight of these the increase was more than 10% of the original value. Three patients showed decreases, all of which were less than 10% of the original values. One patient showed no change.

One of the patients who received control therapy with dextrose showed essentially no change in the one-second vital capacity at any time. Patient 2 showed an increase in the one-second vital capacity after dextrose was given, and this remained essentially the

TABLE 2.—*Results of Pulmonary Ventilation Tests in Patients Treated with Tetracycline*

Patient No.	Total Vital Capacity, L.			1 Sec. Vital Capacity, L.			Maximum Breathing Capacity, L./Min.		
	Initial Observations	After Dextrose	After Tetracycline	Initial Observations	After Dextrose	After Tetracycline	Initial Observations	After Dextrose	After Tetracycline
				Patients with Bronchiectasis					
1	1.6 *	--	2.0 * †	0.85	--	1.1 †	35.0	--	35.
2	2.53	2.47	2.35	1.33	1.95 †	1.93	36.6	40.5 †	39.
3	1.15 *	--	1.05 *	0.99 *	--	0.92 *	34 *	--	19.2 *
4	2.0 *	--	2.0 *	1.4 *	--	1.5 *	--	Not done	--
5	2.73	--	2.57	1.7	--	1.57 †	33.6	--	28.6
7	1.51 *	--	1.8 * †	0.8 *	--	1.05 * †	--	Not done	--
8	2.2 *	--	2.8 * †	2.0 *	--	2.1 *	--	Not done	--
9	1.73 *	--	1.83 *	1.08 *	--	1.08 *	--	Not done	--
10	2.17	2.5	2.37	0.83	0.8	0.8	21.7	21.4	22.0
				Patients with Chronic Bronchitis					
11	2.0	1.67	1.87	0.77	0.72	0.87 †	19.5	19.3	21.7 †
12	2.23	--	2.53 †	1.70	--	2.08 †	54.2	--	69.3 †
13	4.6	--	4.85	3.33	--	3.9 †	103.3	--	114.0 †
14	3.0	--	3.4 †	1.2	--	1.33 †	24.4	--	27.7 †
15	2.4	--	2.77 †	1.2	--	1.38 †	33.3	--	40.8 †

* Only a single determination was made instead of 3.
† Tests showing improvement of 10% or more of the initial values.

TABLE 3.—*Results of Tests of Gas Exchange in Patients Treated with Tetracycline*

Patient No.	Arterial CO_2 Tension (Normal, 38–42 mm. Hg)			Arterial O_2 Tension (Normal, 85–100 mm. Hg)			Alveolar-Arterial pO_2 Difference (Normal, 10–20 mm. Hg)		
	Initial Measurement	After Dextrose	After Tetracycline	Initial Measurement	After Dextrose	After Tetracycline	Initial Measurement	After Dextrose	After Tetracycline
2	37	29 *†	34 *	92	103 †	101	21	15 †	12 †
5	36	--	36	77	--	78	30	--	32
10	45	52	47	81	79	86	29	19 †	19
11	50	50	44 †	63	63	72 †	38	39	36
13	30	--	35	67	--	77 †	48	--	39 †

* Duplicate analyses did not check within ± 3 mm. Hg pCO_2.
† Tests showing improvement of 10% or more of the original values.

same after tetracycline therapy. Patient 11, however, showed a slight decrease after dextrose therapy and a considerable increase after tetracycline therapy.

The maximum breathing capacity was tested on 10 patients. There was an increase in six, and in five the increase was more than 10% of the original value. There was a decrease in two patients of more than 10% of the original value, and the test values remained the same for the other two patients. Among the three patients treated with intravenous dextrose no significant change in the maximum breathing capacity was observed in two patients (Patients 10 and 11). Patient 2 showed an improvement of over 10% after the control period but lost slightly after tetracycline therapy. Patient 11 showed a slight decrease after dextrose therapy, followed by more than a 10% increase after tetracycline therapy.

Improvement of 10% or more of the original value was observed in each of the patients with chronic bronchitis in all of the tests, with the exception of the vital capacity in Patients 11 and 13. This is in decided contrast to the results in the patients with bronchiectasis where improvement of 10% or more of the original values was observed in less than one-third of the tests.

The observations of arterial carbon dioxide and oxygen tensions and alveolar arterial (A-a) differences in oxygen tension in five patients are summarized in Table 3. These included the three patients who received dextrose therapy as a control. The arterial carbon dioxide tension measurements showed no consistent pattern before and after tetracycline therapy; two patients showed an increase, two, a decrease, and the other patient showed no change in this measurement.

In the data on arterial oxygen tension there was a negligible decrease in one case, a negligible increase in one case, and an appreciable increase in three cases. In two of the latter, control therapy had been given; in one the increase appeared after dextrose therapy, whereas in the other the increase did not appear until after the tetracycline therapy.

The alveolar-arterial oxygen tension differences (A-a pO_2) all exceeded the normal range during the first period of observation. The values for Patients 2 and 10 decreased to the normal range after dextrose therapy and remained at essentially the same values after tetracycline therapy. The tests on Patients 5 and 11 showed no significant changes. Patient 13 showed a significant decrease, although not to the normal range. It is not possible to draw any conclusions from these data as to whether increased venous admixture or an abnormal diffusion barrier played a predominant role in these abnormal A-a pO_2 differences. However, since the improvement of arterial pO_2 and alveolar-arterial pO_2 difference was more consistent than the changes in arterial pCO_2, it can be surmised that intrapulmonary gas exchange in these patients was slightly improved during the period of observation without comparable improvement in ventilation.

Comment

In chronic bronchiectasis and chronic bronchitis the infectious process may produce disability in two ways: (1) as a result of the infection itself and (2) as a result of the damage to tissues which follows the infection. Any therapy that is proposed for these patients must be directed at improving one or both of these conditions. Since there is good clinical evidence that patients who have an acute exacerbation of chronic bronchitis or bronchiectasis with high fever and other evidences of toxicity are improved by various antibiotics, it was not the purpose of the present study to confirm or extend these observations. Rather, patients with advanced chronic bronchitis or bronchiectasis were selected who were not in an acute exacerbation of the disease and had little toxicity. Accordingly, measurement of improvement in the infection was extremely difficult.

It is apparent from the data presented in Table 1 that a course of tetracycline given intravenously was able to clear the sputum of H. influenzae, pneumococci, and β-streptococci in every case. M. pyogenes var. aureus appeared in the sputum of two patients during therapy, and in one of these it was present in sufficient numbers so that the sputum remained purulent in appearance. Nevertheless, even in this patient there was a 50% decrease in the amount of sputum, and there was symptomatic improvement in the patient's course for several months after discharge from the hospital.

Where fever was present before tetracycline therapy, it usually disappeared, though three patients showed a slight, transient elevation, presumably from chemical thrombophlebitis. The patients reported in all instances that cough was decreased and they felt better after therapy. It is difficult to judge, however, whether this was due in part to the rest and symptomatic therapy obtained during the period of hospitalization.

The effect of the infection upon pulmonary function is more difficult to measure. At present, we have no physiological tests of the integrity of the walls of the tracheobronchial tree or the effectiveness of the cilia in clearing this area. Studies of ventilation and gas exchange are only indirect indices of these functions. In the present study, they indicate some improvement in the majority of patients, but not consistently or of a degree that was comfortably beyond the variability of the methods themselves.

The present study appears to show that tetracycline administered in doses that will achieve relatively high concentrations in the body fluids will bring about improvement in the bacteriologic state of the sputum and presumably, therefore, of the inflammation in the bronchi. Since the procedure requires hospitalization, it is obviously not recommended for every patient with bronchiectasis, but should be reserved for use during acute exacerbations or in patients who have considerable disability from chronic cough, expectoration of large amounts of sputum, and/or toxic symptoms from infection. If the condition of these patients cannot be improved by simpler measures, the administration of tetracycline by the intravenous route should be considered.

Summary and Conclusions

Ten patients with bronchiectasis and five with chronic bronchitis were treated with intravenous tetracycline for 5 to 10 days in doses of 1 to 1.5 gm. per day for adults and the equivalent for children.

Pathogenic bacteria disappeared from the sputum in every case, although they were replaced by M. pyogenes var. aureus in two cases. In one of these the sputum remained purulent. In all of the others it became clear.

Tests of vital capacity, timed vital capacity, and maximum breathing capacity showed no consistent trend before and after therapy in patients with bronchiectasis. They improved significantly in the five patients with chronic bronchitis.

Improvement in the arterial oxygen tension and in arterial-alveolar oxygen difference was observed in three of five patients

tested, indicating improved intrapulmonary gas exchange. Changes in arterial carbon dioxide tension were equivocal, indicating that no significant improvement in ventilation occurred.

Untoward reactions were confined to thrombophlebitis which subsided in a few days without complication.

It is concluded that intravenous tetracycline therapy improves the infectious process in chronic bronchitis and bronchiectasis, and its use is recommended where simpler measures have failed. Long-term serial studies are needed to determine whether improvement in infection is accompanied by improved pulmonary function.

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University of Illinois College of Medicine, 1853 W. Polk St., (12) (Dr. Dowling).

REFERENCES

1. Mulder, J.: Hemophilus Influenzae (Pfeiffer) as an Ubiquitous Cause of Common Acute and Chronical Purulent Bronchitis, Acta med. scandinav. 94:98-140, 1938.

2. Mulder, J.; Goslings, W. R. O.; van der Plas, M. C., and Lopes Cardoza, P.: Studies on the Treatment with Antibacterial Drugs of Acute and Chronic Mucopurulent Bronchitis Caused by Hemophilus Influenzae, Acta med. scandinav. 143: 32-49, 1952.

3. Hers, J. F. P., and Mulder, J.: The Mucosal Epithelium of the Respiratory Tract in Muco-Purulent Bronchitis Caused by Hæmophilus Influenzae, J. Path. & Bact. 66:103-108 (July) 1953.

4. Allison, P. R.; Gordon, J., and Zinnemann, K.: The Incidence and Significance of H. Influenzae in Chronic Bronchiectasis, J. Path. & Bact. 55:465-475 (Oct.) 1943.

5. Franklin, A. W., and Garrod, L. P.: Chloramphenicol Treatment of Bronchiectasis in Children, Brit. M. J. 2:1067-1069 (Nov. 14) 1953.

6. Allibone, E. C.; Allison, P. R., and Zinnemann, K.: Significance of H. Influenzae in Bronchiectasis of Children, Brit. M. J. 1:1457-1460 (June 23) 1956.

7. Stuart-Harris, C. H.; Pownall, M.; Scothorne, C. M., and Franks, Z.: The Factor of Infection in Chronic Bronchitis, Quart. J. Med. 22:121-132 (April) 1953.

8. May, J. R.: The Bacteriology of Chronic Bronchitis, Lancet 2:534-537 (Sept. 12) 1953.

9. Brown, C. C., Jr.; Coleman, M. B.; Alley, R. D.; Stranahan, A., and Stuart-Harris, C. H.: Chronic Bronchitis and Emphysema: Significance of the Bacterial Flora in the Sputum, Am. J. Med. 17:478-484 (Oct.) 1954.

10. May, J. R.: Antibiotics in Chronic Bronchitis, Lancet 2:899-902 (Oct. 31) 1953.

11. Knox, K.; Elmes, P. C., and Fletcher, C. M.: Chronic Bronchitis: An Attempt to Control Chronic Infection with Hæmophilus Influenzæ by Aerosol Therapy, Lancet 1:120-122 (Jan. 15) 1955.

12. Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Antibiotic Therapy in Infections of the Respiratory Tract: Use of Penicillin, Including Aerosol, Dust, and Diethylaminoethyl Iodide Penicillin; and Aureomycin, Terramycin, and Chloramphenicol in Bronchiectasis, Bronchitis, Sinusitis, Bronchial Asthma and Pulmonary Emphysema, A. M. A. Arch. Int. Med. 90:808-849 (Dec.) 1952.

13. Williams, M. H., Jr.: Pulmonary Function in Bronchiectasis, Washington, D. C., Walter Reed Army Medical Center, Army Medical Science Graduate School, September, 1954.

14. Rawlings, G. A.: Liquefaction of Sputum for Bacteriological Examination, Lancet 2:538-539 (Sept. 12) 1953.

The Influence of the Endocrine Glands on Fatty Acid and Ketone Body Metabolism

FRANK L. ENGEL, M.D., Durham, N. C.

The phenomenon of ketosis has intrigued physicians and biochemists ever since the ketone bodies, acetoacetic acid, β-hydroxybutyric acid, and acetone were identified almost 100 years ago in the urine of patients with diabetic acidosis.[1] The decade beginning in 1930 marked the opening of a period of intense interest in the role of the endocrines in ketosis, sparked by the almost simultaneous discovery and investigation of the ketogenic activity of certain pituitary extracts by Burn and Ling,[2] Anselmino and Hoffman,[3-5] Black, Collip, and Thomson,[6] and Rietti.[7-10] Especially noteworthy during this period was the work in the laboratories of Houssay,[11-13] Long,[14-16] Mirsky,[17-20] Somogyi,[21,22] and Stadie.[23] Progress in this field was impeded to some degree, however, by methodological difficulties, by lack of availability of purified hormones, and by large gaps in knowledge concerning the details of the metabolic processes involved in fat catabolism and anabolism and in ketogenesis itself. Thanks to the brilliant work of biochemists in the past decade these major blocks to progress have been largely overcome, a fact which has stimulated us to reinvestigate certain aspects of the problem of the influence of the endocrines on fatty acid and ketone body metabolism.

The elucidation of the pathways of fat metabolism was initiated by the demonstration of fatty acid catabolism in the cell-free system by Leloir and Munoz, in 1939,[24] and brought to fruition by the work of Lehninger,[25-27] Lipmann,[28] Lynen,[29] Ochoa,[30] Green,[31] and others who rapidly worked out the details of the metabolic steps and enzyme systems involved in fat synthesis and degradation. While there are still many biochemical questions to be answered, the status of the field is now such as to allow for a much more rational interpretation of the phenomenon of ketosis and of the influence of hormones thereon.

The chief ketone body is acetoacetic acid; from this is derived β-hydroxybutyric acid by reduction and acetone by decarboxylation. Acetoacetic acid is a normal intermediary in fat metabolism, but it ordinarily exists only in a transitory state as acetoacetyl-CoA in the anabolic and catabolic pathways of fatty acids (Fig. 1). Only the liver possesses an enzymatic organization which permits both the formation and the release of free acetoacetate into the blood stream.

The precursor of acetoacetyl-CoA (coenzyme A) is acetyl-CoA. This may be derived from a number of sources, but particularly from the catabolism of fatty acids. The latter occurs in series of steps illustrated on the right side of Figure 1. Each turn of the "fatty acid cycle" results

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Departments of Medicine and Physiology Duke University.

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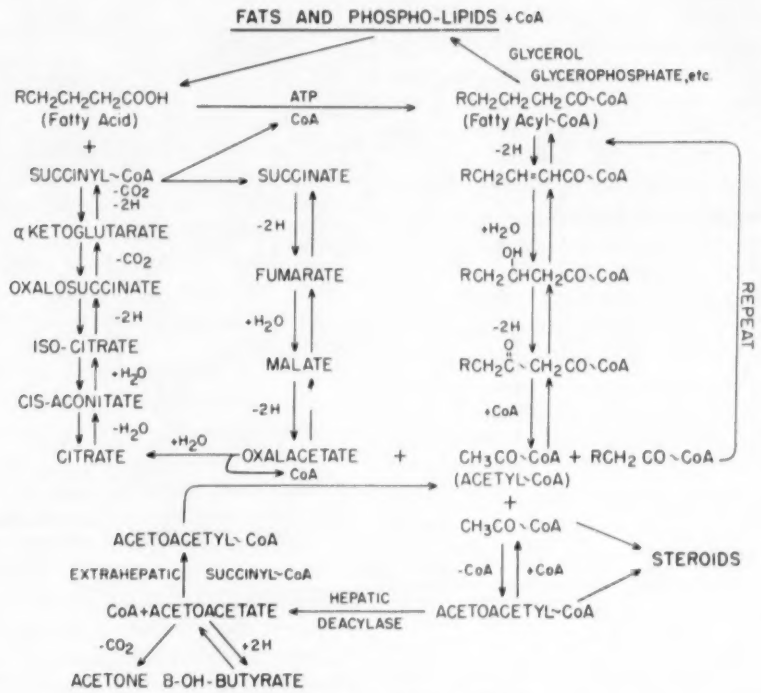

Fig. 1.—Pathways of fat metabolism.

in the release of a two-carbon compound, acetyl-CoA. If this is not further oxidized via the Krebs cycle, illustrated on the left side of the diagram, or resynthesized to fat, it may condense with another molecule of acetyl-CoA to form acetoacetyl-CoA, with the release of one molecule of CoA. In the liver, the acetoacetyl-CoA is deacylated through the influence of the enzyme deacylase and released into the hepatic vein, freeing another molecule of CoA. The extrahepatic tissues possess a very active enzyme system for recombining CoA with acetoacetate, which is brought to them via the blood stream or formed in situ. The CoA may be donated by succinyl-CoA in the Krebs cycle. The liver lacks this enzymatic mechanism for reconstituting acetoacetyl-CoA, and hence is the only organ which may present significant quantities of ketone bodies to the blood stream. The acetoacetyl-CoA formed in the extrahepatic tissues may be oxidized via the Krebs cycle or may be involved in synthetic pathways.

In final analysis, ketone metabolism is an indirect reflection of the metabolism of acetyl-CoA, which in turn may be looked upon as the hub of intermediary metabolism (Fig. 2). This fact gives added interest to the study of ketone metabolism under various physiological and pathological circumstances. Acetyl-CoA may be derived from carbohydrate metabolism via pyruvate, from fat catabolism by successive β-oxidation of fatty acids, and from protein through various possible pathways, as indicated in the Figure. In turn the metabolism of acetyl-CoA may follow multiple alternate pathways. First of all acetyl-CoA may be oxidized to completion in the Krebs cycle after condensation with oxalacetate to form citrate. With each turn of the cycle a molecule of acetyl-CoA is burned completely, oxalacetate is regenerated, and a considerable

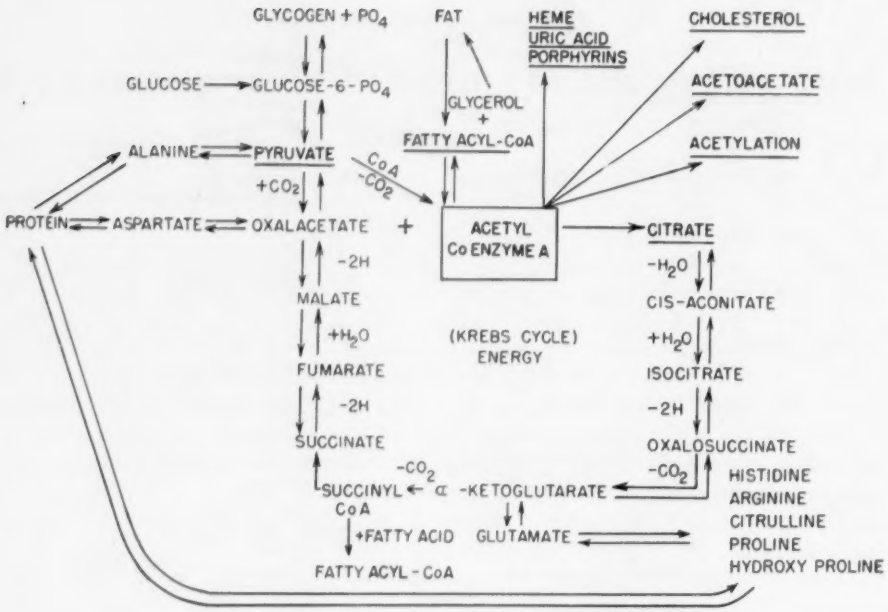

Fig. 2.—Acetyl-CoA as the central point of metabolism.

amount of energy is made available. Acetyl-CoA may also follow a synthetic path to longer-chain fatty acids and eventually neutral fat, phospholipids, etc. (Fig. 1). This process depends on a continuing metabolism of glucose via the glycolytic pathway, the DPN.2H generated thereby favoring fatty acid synthesis. Finally, acetyl-CoA is an intermediary in the synthesis of cholesterol and steroid hormones, purines, heme, and porphyrins and is utilized in acetylation reactions.

Hepatic ketone body production may be interpreted in terms of a balance between the rates of production of acetyl-CoA from fat catabolism on the one hand and of disposal by oxidation via the Krebs cycle or by reduction and synthesis to fat on the other hand. Whenever its rate of formation exceeds that of its removal by oxidation or reduction, two molecules of acetyl-CoA may condense to form acetoacetyl-CoA, and this, as well as additional acetoacetyl-CoA derived directly from fat catabolism, may be released into the hepatic vein as free acetoacetate through the action of the enzyme deacylase (Fig. 1). Since glucose utilization via glycolysis makes available DPN.2H for fat synthesis, it can be seen why utilizable carbohydrate exerts an antiketogenic action and why ketosis occurs during carbohydrate deprivation and in diabetes mellitus.

The level of blood ketone bodies is largely determined by their rate of production and release by the liver, since their rate of utilization by the peripheral tissues apparently does not fluctuate within nearly as wide a range as does the rate of production. Renal function is another factor in ketosis, its major importance being that the ability to excrete ketone bodies may vary under different physiological and pathological circumstances. Ketonuria thus may not always be an adequate reflection of ketonemia.

With this background we may proceed to consider some aspects of the hormonal control of ketone metabolism. This has been a major research interest in this laboratory for several years, and hence this report will be oriented primarily from the vantage point of our own studies, some of which are as yet unpublished.

Diabetes Mellitus and Insulin

The occurrence of ketosis and its alleviation by insulin in diabetes mellitus is so well known that it needs little discussion. The intensity of ketosis in diabetes far exceeds that of any other pathological situation. It is the only type of ketosis in which a really serious disturbance in acid-base balance occurs and in which the accumulation of ketone bodies may result in notable symptoms, i. e., coma. In terms of current concepts of the metabolic lesion in diabetes mellitus, the basis for the ketosis seems reasonably clear. In the absence of insulin, glucose utilization is inhibited either in its transfer through the cell membrane or in its phosphorylation to glucose-6-phosphate. Lipogenesis from carbohydrate is reduced sharply in the diabetic animal, presumably by a specific block in the conversion of acetyl-CoA to fat,[32] and the final oxidation of glucose via the Krebs cycle is depressed. Fat is mobilized to the liver and is catabolized at an accelerated rate. Stadie has recently reviewed the evidence suggesting that the catabolic pathway of fat metabolism may diverge at some point from the anabolic pathway and that the block in fatty acid synthesis in diabetes may be between acetyl-CoA and butyryl-CoA[33]. The combination of impaired glucose utilization and glycolysis, inhibition of fat synthesis, and accentuation of fat catabolism makes for the maximal possible potential accumulation of acetyl-CoA in the liver. By the mechanisms already described the excess acetyl-CoA drains from the liver as acetoacetate. Insulin corrects the basic defect in carbohydrate utilization and fat synthesis and thus overcomes the ketosis, provided adequate carbohydrate is available for metabolism.

In the normal organism the direct metabolic influence of insulin in ketone metabolism must be distinguished from the secondary reaction to the hypoglycemia. The immediate effect of insulin is to lower the level of blood ketones as the blood sugar level is falling, and one may assume that this effect is brought about through a reversal of the biochemical mechanisms just described. However, once hypoglycemia is established the decline in blood ketone levels comes to a halt and is followed in several hours by an increase beyond the initial values, a sequence of events which has been known for many years.[34] In the normal subject the time of the ketosis corresponds to the period of recovery from hypoglycemia. This posthypoglycemic ketonemia is due to an increased hepatic production of ketone bodies. Employing the technique of hepatic vein catheterization, we have made a quantitative estimate of the rate of splanchnic production of ketone bodies in man by simultaneously determining the hepatic vein-femoral artery blood ketone-body level difference and the estimated hepatic blood flow by the sulfobromophthalein method.[35] Five hours after a brief episode of hypoglycemia induced in normal man by the intravenous injection of 0.1 unit of insulin per kilogram of body weight there is a fivefold increase in ketone body production by the liver (Table).[36] This observation lends experimental support to the clinical experience that insulin hypoglycemia may initiate ketosis in the diabetic patient. In the same experiment an infusion of sodium octanoate, an eight-carbon fatty acid and known ketone body precursor, was done during the period of recovery from hypoglycemia to determine whether hypoglycemia resulted in an accelerated conversion of a fatty acid to ketone bodies. As is apparent from the Table, there was no greater increment in ketone-body

Net Splanchnic Ketone Body Production in Man After an Overnight Fast and Five Hours After Intravenous Administration of Insulin *

Subject Group	N.S.K.P., μM Acetone/Min./M.²		
	Control	During Na Oct.	Δ+
Control	34.0 ± 5.20	158.0 ± 6.86	114.0 ± 10.34
Hypoglycemic	160.7 ± 46.0	266.3 ± 43.5	105.6 ± 27.8
P values	<0.01	<0.01	>0.5

* 0.1 unit of insulin per kilogram of body weight.

production over the basal values in hypoglycemic subjects as compared to their controls, suggesting that the action of insulin hypoglycemia is not directly on fatty acid catabolism. This result contrasts with the action of a pituitary ketogenic factor to be described later which did result in a greater yield of ketone bodies from infused octanoate in the rat.[37]

A metabolic basis for hypoglycemia ketosis may be visualized readily in terms of current concepts of intermediary metabolism. Hypoglycemia, whether induced by insulin, phloridzin, or starvation, calls forth a metabolic adjustment which may be viewed teleologically as designed to restore the blood sugar as rapidly and effectively as possible to maintain the metabolic integrity of the central nervous system. This reaction to insulin hypoglycemia is essentially the same as that during fasting except that the former is of necessity more intense and is telescoped in time. The first response is a release of glucose from the preformed stores of glycogen in the liver. Epinephrine facilitates this reaction, which is relatively short-lived, since the liver glycogen stores are rapidly depleted. Secondly, glucose utilization, particularly for fat synthesis, is reduced to a minimum in all tissues other than the central nervous system. An impaired tolerance to glucose is readily demonstrated following insulin hypoglycemia. Protein catabolism is accelerated, presumably for the purpose of gluconeogenesis. In the rat an increase in nitrogen metabolism has been shown to occur within three hours of the induction of hypoglycemia.[38] Finally, fat catabolism is increased and with it ketosis occurs; the former is reflected in a lowering of the R. Q. This combination of metabolic events may be interpreted as "diabetes in miniature" and, indeed, in fasting has long been known as hunger or starvation diabetes. The ketosis is much less intense than in diabetic ketosis but presumably is brought about by somewhat similar mechanisms, i. e., the combination of diminished glucose utilization, impaired fat synthesis, and accelerated fat catabolism all leading to a surplus of acetyl-CoA to condense to acetoacetyl-CoA, which in turn is released into the hepatic vein as acetoacetate. In contrast to diabetic ketosis, however, it is promptly alleviated by glucose administration.

There are reasons to believe that certain features of this metabolic reaction might be moderated by endocrine secretions, since the total picture of starvation diabetes does not develop in the absence of the adenohypophysis, and/or the adrenal cortex and the response may be exaggerated in the absence of the pancreas. Moreover, an increased secretion of metabolic factors from the pituitary,[39] of adrenal cortical steroids,[40] and of epinephrine [41] has been reported during insulin hypoglycemia, and it is well known that insulin secretion by the pancreas is depressed by hypoglycemia.[42] The concept that the endocrines are specificially involved in the ketosis of fasting and insulin hypoglycemia will now be examined.

The Adrenal Medulla

Since an epinephrine discharge occurs early in response to hypoglycemia, it may be involved in the ketonemic response, particularly since the adrenal medulla has recently been implicated in certain types of fat mobilization to the liver.[43] The adrenal medulla, the chief source of epinephrine, is not essential for ketosis, since the adrenodemedullated rat still exhibits a ketonemic response to insulin hypoglycemia.[44] Epinephrine itself has a depressing effect on ketonemia in the rat,[45] although in other species both no effect and a ketonemic response have been described.[46]

The Adrenal Cortex

Early reports on the influence of adrenalectomy on ketosis were contradictory, largely because ketonuria was used as the basis for estimation of ketosis and the influence of the abnormal renal function of adrenal insufficiency was not taken into account. Adrenalectomy reputedly depressed ketonuria, but when blood ketone levels were

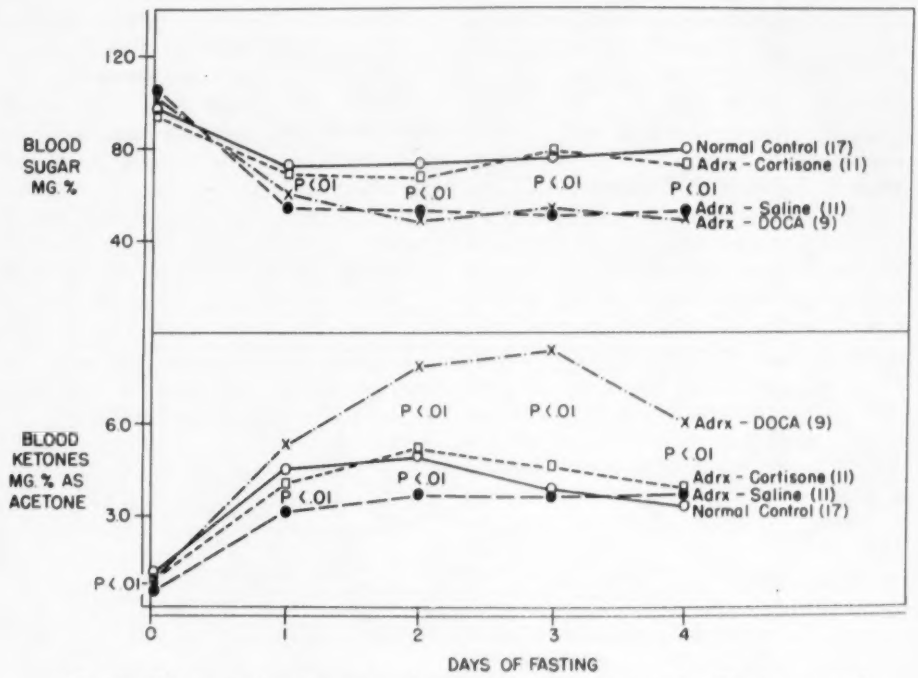

Fig. 3.—Effect of adrenalectomy on fasting glycemia and ketonemia. Blood sugar and ketone body levels in normal and adrenalectomized rats during a four-day fast. Note the increased ketonemia in the rats maintained on desoxycorticosterone acetate (Doca) and the decreased ketonemia in the saline-treated rats despite comparable hypoglycemia. Cortisone restores glycemia and ketonemia to normal.

measured it was established that these were not as low as anticipated from the urine values.[20,47] Our studies have indicated that a failing peripheral circulation inhibits ketonemia and suggest that this factor may have been responsible for the difficulty in estimating the degree of ketonemia due specifically to the lack of adrenal steroids.[48] Indeed, if adrenalectomized rats are kept in optimal condition with sodium chloride and desoxycorticosterone acetate (Doca) during a prolonged fast, they exhibit a slightly but significantly greater ketonemia than do normal rats (Fig. 3).[49] This ketosis is reduced to normal by cortisone treatment. Desoxycorticosterone acetate itself has no effect on ketonemia in normal rats and hence presumably is not responsible for the ketosis observed in the desoxycorticosterone-acetate-maintained adrenalectomized rats. Not only is there enhanced ketonemia in the fasted adrenalectomized rat protected with desoxycorticosterone acetate and salt, but recent data also indicate that the same type of rat can still respond to insulin hypoglycemia with a rise in blood ketones, despite the depressing effect of hypoglycemia on the circulation of the adrenalectomized rat.[44]

It is thus apparent that the adrenal cortex, like the medulla, also is not essential for the ketosis of fasting or hypoglycemia, even though their secretion is increased by these stimuli. Indeed, as first shown by Kinsell, in man with cortisone and a slow infusion of corticotropin (ACTH),[50] and confirmed by us, in the rat,[49,51] cortisone and related compounds actually inhibit fasting ketosis (Fig. 4). Cortisone and hydrocortisone also suppress the ketosis associated with cold stress[51] and intoxication with sodium fluoroacetate, a Krebs cycle poison,[52] but they do not modify the ketonemia secondary

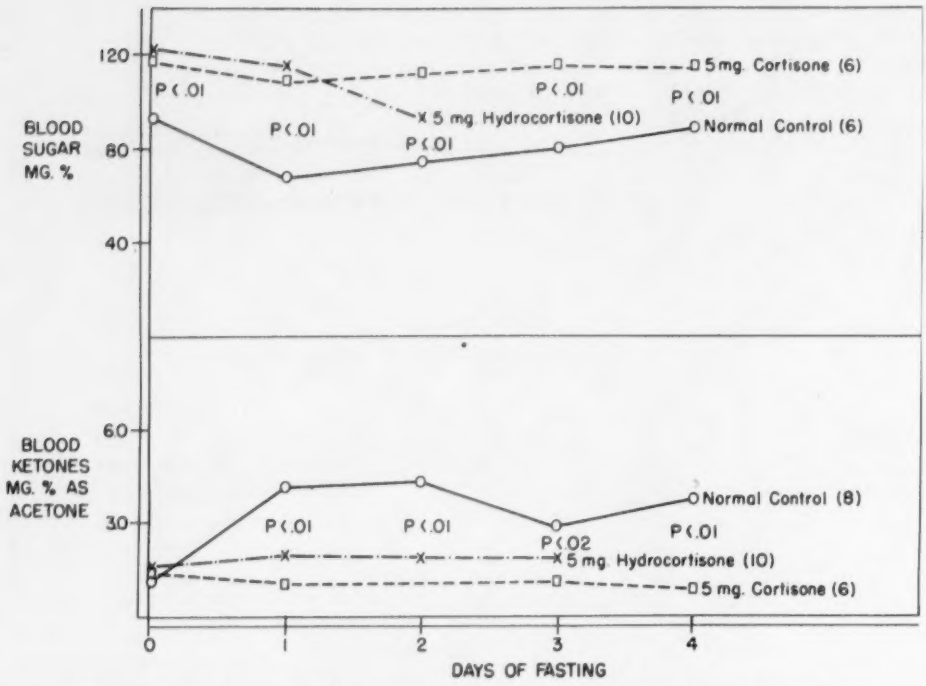

Fig. 4.—Suppression of fasting ketosis by cortisone and hydrocortisone in normal rats. Note elevated blood sugar levels in corticoid-treated rats.

to insulin hypoglycemia in either man [36] or the rat [44] or that due to certain pituitary extracts in the rat.[45] It is thus apparent that the adrenal cortex not only is not essential for ketosis, but that the glucocorticoids may, under certain circumstances, actually inhibit ketosis.

The possible mechanisms by which the adrenal cortex influences ketone metabolism are difficult to formulate, largely because there are still many gaps and certain contradictions in our knowledge of the role of the adrenal cortex in intermediary metabolism. The largest area of disagreement relates to the role of the adrenal cortex in fat anabolism and catabolism. Some of the discrepancies undoubtedly hinge on differences in experimental conditions and techniques. Thus the data of Welt and Wilhelmi [53] indicate that adrenalectomized rats fed a fat-free high-carbohydrate diet have a higher rate of lipogenesis from carbohydrate than controls but that their rate of fat utilization is also considerable. This, as well as the observation that adrenalectomy and hypophysectomy restore lipogenesis to normal in the diabetic animal,[54] indicates that adrenal hormone lack has a favorable influence on lipogenesis. This interpretation, however, is not supported by the studies of Lipsett and Moore [55] and Perry and Bowen,[56,57] which present evidences of impaired lipogenesis from acetate and no disturbance in fatty acid catabolism in the livers of adrenalectomized rats.

In either case, one can offer a reasonable explanation for the mild ketosis of fasting in the adrenalectomized animal and the suppression of ketosis by glucocorticoids. In the former, the stage is set by the rapid depletion of liver glycogen during fasting, due presumably to continuing ample glucose utilization without compensatory gluconeogenesis from protein catabolism as occurs

normally during a fast. As the fast continues, lipogenesis must decline, and fat catabolism is at least as great, or greater, than normal. Both these factors contribute to ketogenesis. If in addition we assume that the accelerated protein catabolism which occurs in the normal organism can inhibit ketosis to some degree by contributing intermediaries to the Krebs cycle, it becomes apparent why ketonemia in the adrenalectomized rat finally exceeds the normal as the fast continues.

The antiketogenic effect of the glucocorticoids may be interpreted in terms of their action in shifting the balance of fat metabolism toward a net accumulation of fat, regardless of whether this is brought about by an inhibition of fat synthesis and fat catabolism, with the latter inhibition exceeding the former, or whether fat synthesis may actually be stimulated. In any case, the consequence of such a shift would be a decreased supply of acetyl-CoA and acetoacetyl-CoA from fat catabolism. At the same time the accelerated rate of gluconeogenesis associated with glucocorticoid action during fasting maintains liver glycogen and also keeps up a supply of Krebs cycle intermediaries from amino acids to help "drain off" acetyl-CoA into the cycle despite a simultaneous mild inhibition of glucose utilization. Cortisone has diabetogenic activity, but the bulk of evidence indicates that it causes a type of diabetes which is primarily due to overproduction of carbohydrate,[58] in contrast to the predominantly "underutilization" diabetes of insulin deficiency.[59] It is of interest that the diabetes of Cushing's disease is rarely complicated by ketosis. Moreover, corticotropin or cortisone has been given to diabetic patients and has exacerbated glycosuria without inducing ketosis.[60] Indeed, in some cases ketosis has even been diminished by cortisone treatment.

The demonstration by Kinsell[50] that a continuous infusion of corticotropin inhibited fasting ketosis in man seemed at first to be a paradox, since corticotropin had been reported to be ketogenic in the rat.[61] Studies in this laboratory at first heightened the controversy, because it was found that corticotropin injected into rats four times daily had no effect whatsoever on ketonemia during a four-day fast, even though cortisone in a comparable experiment completely suppressed ketosis.[51] Eventually, however, the contradictory data were explained by the discovery that in acute experiments corticotropin produced an immediate rise in blood ketones and that this ketonemia occurred even in the total absence of the adrenal glands.[62] In short, the previously described ketogenic effect of corticotropin was not mediated by corticoids from adrenal stimulation but was due either to an extra-adrenal metabolic effect of corticotropin or to contamination of the corticotropin with a ketogenic principle from the pituitary. Kinsell's results, in turn, were obviously due to the mode of administration of corticotropin employed by him. The slow infusion resulted in a strong stimulation of the adrenal cortices with a minimal dose of the pituitary factor. These observations lead us to a consideration of pituitary factors in ketosis.

Adenohypophysis

It is now well known that certain pituitary extracts not only induce ketosis but also have other interesting metabolic effects. These include mobilization of fat to the liver (adipokinesis), hyperlipemia, depression of the R. Q., hypoglycemia in the animal which has fasted, and anti-insulin activity.[63] As pituitary extracts became more purified, these various metabolic activities became increasingly associated with the fraction possessing growth activity, and, indeed, most investigators are of the opinion that they are specific properties of growth hormone. On the other hand, extensive chemical and biological studies in at least two laboratories have yielded evidence to indicate that the metabolic activities noted above may be as much or more a property of a protein or peptide molecule that behaves chemically more like corticotropin than

somatotropin.[64,65] These metabolic activities of corticotropin are clearly not mediated by adrenal cortical stimulation, being demonstrable in adrenalectomized animals. However, it is not established whether they represent properties of the same molecule or portion thereof which is responsible for the corticotropic activity per se. Preliminary data suggest that ketogenic and adipokinetic activities may persist after chemical treatment which abolishes adrenal ascorbic-acid-depleting activity. Furthermore, recent studies have shown that of four peptides derived by peptic digestion of oxidized cellulose (Oxycel) corticotropin and possessing corticotropic activity, only two have ketogenic activity.[45] The ketogenic activity does not seem to represent contamination with growth hormone per se, since chemical treatment which destroys the growth-promoting and diabetogenic effects of growth hormone does not eliminate the ketogenic response to either corticotropin or growth hormone.[45]

The problem of the nature of the pituitary factor(s) concerned with fat mobilization and ketosis is further confounded by the fact that thyroid-stimulating hormone also has these properties and has, indeed, been considered by some as the fat-mobilizing and ketogenic hormone.[66,67] It is apparent that while all investigators agree that the adenohypophysis influences fat metabolism, there is at present no agreement concerning the identity of the factor or factors involved. From studies in our laboratory we are led to the preliminary view that growth hormone, corticotropin, and thyrotropin each independently have ketogenic activity. It remains to be established whether the ketogenic and other metabolic activities of different pituitary preparations represent true physiological properties of hormones or whether some of all might be artefacts resulting from the chemical manipulation of pituitary proteins and peptides. They may depend on specific amino acid sequences which endow the whole or a fragment of the original hormone molecule with these biological actions. Precedent for such a concept has just been published by Geschwind et al.,[68] who showed that melanocyte-stimulating hormone (MSH) and corticotropin have a certain amino acid sequence in common. They suggest that the latter might be responsible for intermedinlike activity of corticotropin preparations.

In view of the fact that the adenohypophysis apparently secretes a substance or substances which stimulate ketosis, and since the adrenal cortex and medulla are not necessary for the acute ketosis of hypoglycemia, it has seemed quite reasonable to postulate that the pituitary gland is the endocrine mediator in this response. This is particularly logical, since it has been considered well established that the hypophysectomized animal does not readily develop ketosis. It came as a surprise, therefore, to find that the hypophysectomized rat developed ketonemia quite as well as the normal animal during and following hypoglycemia (Fig. 5).[44] Moreover, when the proposition that the ketosis does not develop during a fast in the absence of the hypophysis was reexamined, it was found that this is true only during a short fast; after 72 hours the hypophysectomized animal exhibits greater ketonemia than the intact animal (Fig. 6). In the normal rat the peak of ketonemia occurs by about the 48th hour; in the hypophysectomized and in the adrenalectomized rat ketonemia tends to increase progressively during the fast. The ketosis in the hypophysectomized rats is associated with greater and more sustained hypoglycemia than in the normal animal. The fall in ketone levels in the normal fasting animal corresponds with the phase of rising blood sugar (and presumably of liver glycogen), and hence there are reasons to suspect that the adrenal cortex might be responsible for the metabolic adjustment, since these changes do not take place in the absence of the adrenal cortex. On the other hand, however, Tepperman and Tepperman[69] found that ketone body production by liver slices from hypophysectomized rats was depressed.

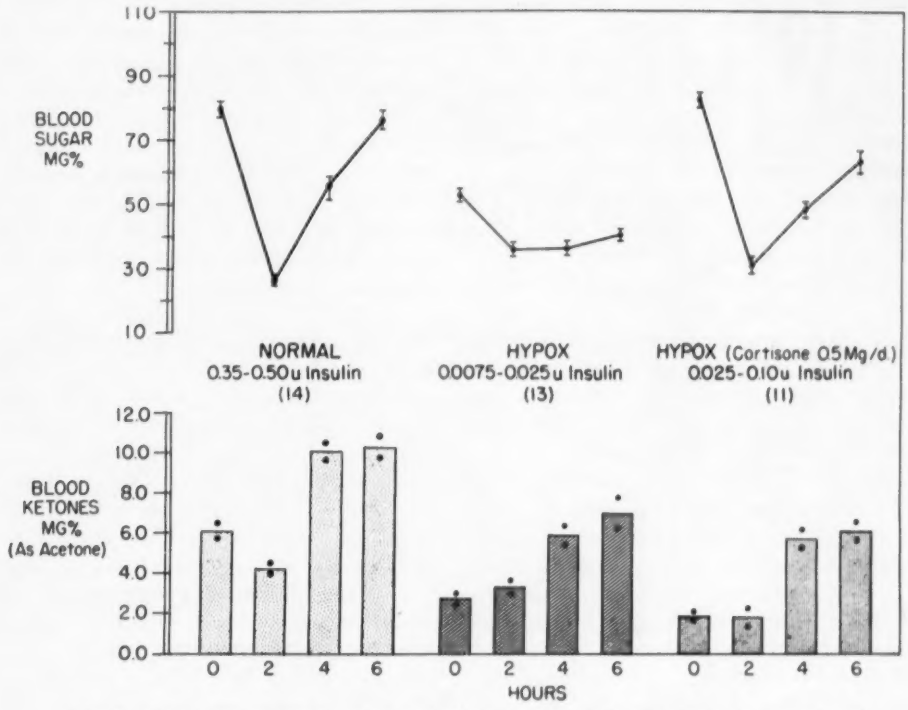

Fig. 5.—Blood ketone levels during and following insulin hypoglycemia in normal and hypophysectomized rats. Although the absolute levels of ketone bodies are lower in the hypophysectomized rats, the increment from the starting level after hypoglycemia was not significantly different in the three groups. Note the fall in ketone bodies at two hours in the controls. This did not occur in the hypophysectomized rats.

During the first 15 days after hypophysectomy ketogenesis could be restored by treatment of the rats with growth hormone. Beyond 30 days after hypophysectomy, cortisone and growth hormone were necessary to restore ketogenesis. Our experience contrasted with Tepperman's for hypophysectomized rats showed an even greater ketonemic response 135-165 days after operation than occurred 11-58 days after operation. The rats recently operated on exhibited more weight loss during fasting, which we interpret as indicating the persistence of some adrenal function. Later, when adrenal atrophy was complete, ketosis was greater and weight loss less during the fast. Bondy and Wilhelmi [70] introduced another parameter into this problem when they found that thyroid treatment restored to normal the low ketogenic potentialities of the liver slice from the hypophysectomized rat. Our own data on the influence of thyroid treatment on ketosis in the hypophysectomized rat are indecisive.

These data appear to be at variance with earlier reports showing that hypophysectomy suppressed fasting and phloridzin-poisoning ketosis.[12] However, examination of the data indicates that the discrepancy is not as great as it seems. In no previous study was a prolonged fast carried out, the longest on record in which blood ketone levels were measured being only 36 hours.[71] In this study ketonemia was the same in the controls and the hypophysectomized animals at this time, even though the latter lagged behind the controls prior to this. In our study on the ketosis of the hypophysectomized rats, ketonemia did not clearly exceed that of the controls until after 72 hours. More difficult

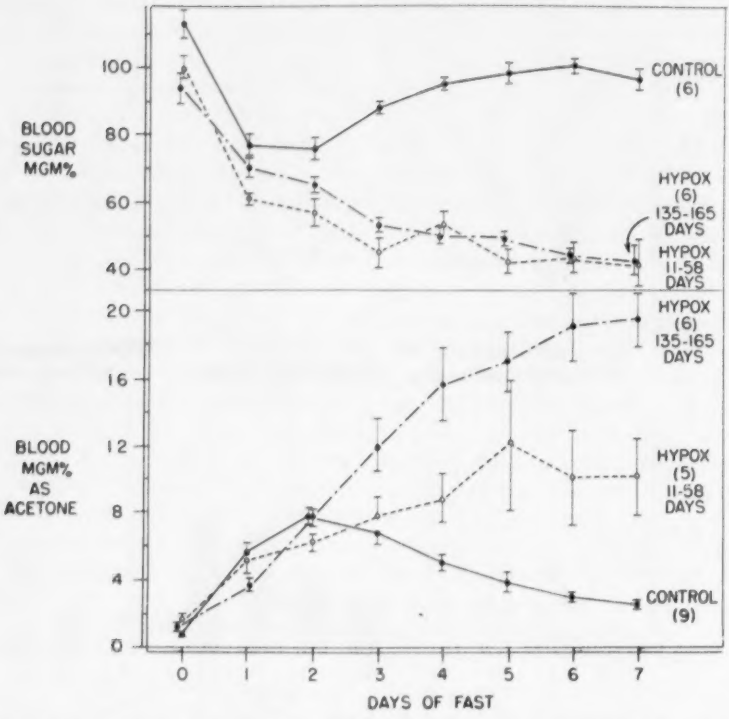

Fig. 6.—Blood sugar and ketone values during a seven-day fast in normal and hypophysectomized rats. Note the inverse relationship between glycemia and ketonemia and the greater ketonemia in the rats that had been hypophysectomized the longest.

to reconcile with these results are the well-established data of Houssay, showing that hypophysectomy abolishes the ketosis of pancreatic diabetes.[11]

The mechanism(s) by which pituitary factors induce ketosis have not been elucidated. There are a number of possibilities which have been considered in detail elsewhere[65]; the problem is complicated by the question of whether or not there are several different ketogenic pituitary factos. However, they all seem to have one property in common, i. e., they also cause a mobilization of fat from the periphery to the liver, thereby providing an increased substrate for ketone production in that organ. In the case of growth hormone the fat accumulation in the liver is preceded by an increase in the blood neutral fat content.[72] The same agent lowers the R. Q., inhibits glucose utilization for fat synthesis and oxidation, stimulates fat catabolism, blocks insulin action, and promotes protein anabolism, all of which would be expected to throw the balance in favor of ketone body production. Indeed, with respect to the last and specific action of growth hormone, it might be noted that under most circumstances of rapid protein synthesis, as in childhood, pregnancy, lactation, and the anabolic phase of convalescence, ketosis develops more readily than normally during fasting. This may be a reflection of the fact that under these circumstances the metabolic machine is geared to a rapid breakdown of fat and to a slowed rate of protein breakdown and gluconeogenesis.

The ketogenic factor which is chemically associated with corticotropin but does not act through the adrenal cortex likewise promotes fat mobilization and also may have a direct effect on fatty acid catabolism and

on ketone body production per se.[37] This was shown in a study in which pretreatment with a single dose of corticotropin resulted in a significantly greater increase in blood ketones during an infusion of sodium octanoate in the rat than would be expected from either the octanoate itself or the hormone. Comparable studies have not been done with purified growth hormone to determine whether it has a similar action on fatty acid metabolism. Corticotropin also prevented the antiketogenic effect of a glucose load. Like growth hormone, corticotropin may also lower the blood sugar during fasting, but this reaction is not responsible for the ketosis, since the latter precedes the hypoglycemia.[62] It also improves carbohydrate tolerance during an intravenous dextrose tolerance test,[37] possibly by promoting glycogen storage in muscle, since there are evidences that it may have an anti-insulin effect in other regards.[64]

The mechanism by which thyroid-stimulating hormone promotes fat mobilization and ketosis is even less well understood. The thyroid is not necessary for this response. Lotspeich and Petersen consider the lowering of the liver glycogen and blood sugar by this material as well as growth hormone to be important for the ketosis.[66, 67]

The observation that the hypophysectomized rat eventually exhibits a brisk ketosis during fasting or after insulin hypoglycemia requires some revision of our notions concerning the role of the adenohypophysis in ketone metabolism, as well as of our concepts concerning the specificity of the ketogenic response. At first it would seem paradoxical that both excess and deficiency of pituitary hormones should be associated with ketosis. However, more sober thought brings us to the realization that this finding is entirely consistent with the basic principle of endocrinology, namely, that the hormones do not initiate or stop metabolic reactions but simply modify their rates. The fasting hypophysectomized animal becomes profoundly hypoglycemic, depleting its muscle and liver glycogen stores, and at the same time has difficulty in mobilizing protein rapidly enough for gluconeogenesis because of adrenal insufficiency. Under these circumstances this carbohydrate-deprived animal has little choice but to draw on its fat stores, which may be ample until fasting, but even these cannot be oxidized completely in the liver because of carbohydrate lack;

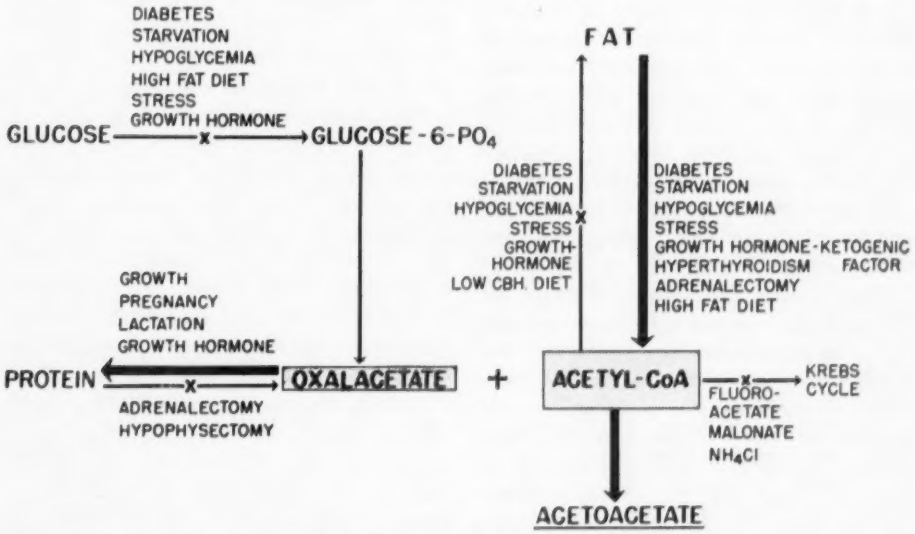

Fig. 7.—Mechanisms of ketogenesis.

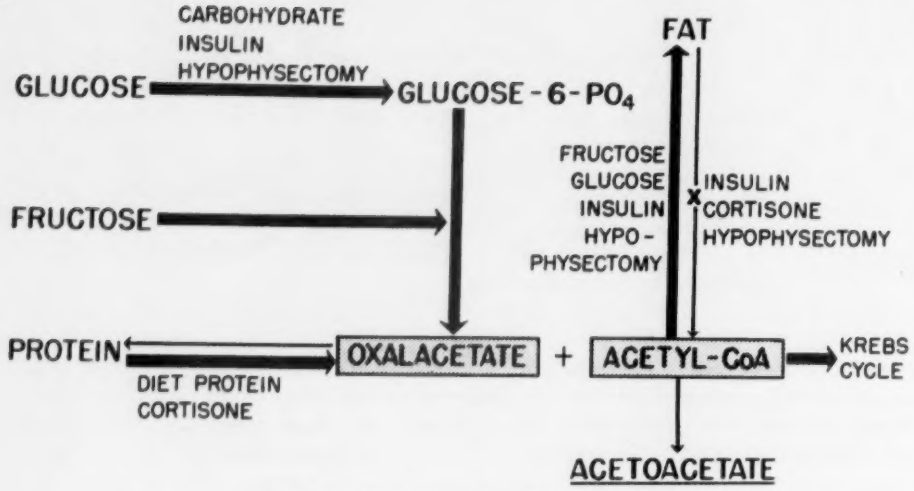

Fig. 8.—Mechanisms of antiketogenesis.

ketosis is the consequence. It is important to emphasize that the ketosis still develops more slowly than normal and that in terms of the magnitude of the hypoglycemic stimulus the degree of ketosis may likewise still be less than normal, a conclusion entirely consistent with the basic principle of endocrinology just stated. Indeed, a more appropriate control for the hypophysectomized rat might be the intact phloridzinized rat with comparable hypoglycemia. It might be predicted from data already available that the normal animal during a prolonged fast would show a marked increase in ketosis during phloridzin hypoglycemia, while the hypophysectomized rat would show little or no change beyond that already noted during the fast.

Some of the endocrine and nutritional factors which influence ketogenesis and antiketogenesis in the liver are depicted in Figures 7 and 8. These diagrams reduce the phenomenon of ketosis to its simplest terms, i. e., the balance between production and utilization of acetyl-CoA by diverse pathways. Ketogenesis is represented by the situation in which there is a theoretical excess of acetyl-CoA, which "drains off" as acetoacetate. Conversely, antiketogenesis follows when the metabolic pattern favors utilization of acetyl-CoA by fat synthesis and oxidation in the Krebs cycle. As indicated in the diagrams, nutritional and hormonal factors may influence different steps in this metabolic picture directly or indirectly and in diverse ways.

Summary

Current concepts of intermediary fat metabolism and ketogenesis are reviewed.

The mechanisms involved in the ketosis of diabetes mellitus, fasting, and insulin hypoglycemia and the antiketogenic action of glucose and insulin are discussed.

The possible roles of the endocrine glands in fasting and insulin hypoglycemia ketosis are reviewed. Neither the adrenal medulla, the adrenal cortex, nor the hypophysis is essential to the development of ketosis during fasting or hypoglycemia. Glucocorticoids suppress the ketosis resulting from fasting, cold stress, and fluoroacetate poisoning, but not that due to insulin hypoglycemia or ketogenic pituitary extracts.

Growth hormone, thyrotropin, and corticotropin possess ketogenic and adipokinetic action, the latter independent of the adrenal cortices. The significance of multiple ketogenic factors and their possible modes of action are considered. The hypophysecto-

mized rat develops greater ketosis and more hypoglycemia than does the normal rat during a seven-day fast.

Department of Medicine, Duke University School of Medicine.

REFERENCES

1. Campbell, J., and Best, C. H.: Symposium on Diabetes: Physiological Aspects of Ketosis, Metabolism 5:95, 1956.

2. Burn, J. H., and Ling, H. W.: The Excretion of Acetone Bodies on a Fat Diet as Affected by the Injection of Pituitary (Anterior Lobe) Extract and by Pregnancy, Quart. J. Pharm. & Pharmacol. 6:31, 1933.

3. Anselmino, K. J., and Hoffman, F.: Das Fettstoffwechselhormon des Hypophysenvorderlappens: I. Nachweis, Darstellung und Eigenshaften des Hormons, Klin. Wchnschr. 10:2380, 1931.

4. Hoffman, F., and Anselmino, K. J.: Das Fettstoffwechselhormon des Hypophysenvorderlappens: II. Stoffwechselwirkungen und-regulationen des Hormons, Klin. Wchnschr. 10:2383, 1931.

5. Anselmino, K. J., and Hoffman, F.: Zur Darstellung des Fettstoffwechselhormons des Hypophysenvorderlappens, Endokrinologie 17:1, 1936.

6. Black, P. T.; Collip, J. B., and Thomson, D. L.: The Effect of Anterior Pituitary Extracts on Acetone Body Excretion in the Rat, J. Physiol. 82:385, 1934.

7. Rietti, C. T.: Variaciones de la cetonuria por inyección de extracto alcalino de lóbulo anterior de hipófisis, Rev. Soc. argent. biol. 10:136, 1934.

8. Houssay, B. A., and Rietti, C. T.: Acción cetonemiante del extracto ánterohipofisario en las insuficienciasendocrinas de la rata, Rev. Soc. argent. biol. 13:209, 1937.

9. Foglia, V. G., and Mazzocco, P.: Acción del extracto ánterohipofisario sobre la grasa hepática y muscular, Rev. Soc. argent. biol. 13:301, 1937.

10. Rietti, C. T.: Elevación cetonémica por extracto ánterohipofisario en el perro, Rev. Soc. argent. biol. 13:312, 1937.

11. Houssay, B. A.: Functions of the Pituitary Gland, New England J. Med. 214:971, 1936.

12. Rietti, C. T.: Ketosis in the Pancreatic and Phlorrhizin Diabetes of Hypophysectomized Dogs, J. Physiol. 77:92, 1932.

13. Foglia, V. G.; Gerschman, R.; Marenzi, A. D.; Munoz, J., and Rietti, C. T.: La agravación de la diabetes pancreática por el extracto alcalino del lóbulo anterior de hipófisis, Rev. Soc. argent. biol. 13:83, 1937.

14. Long, C. N. H., and Lukens, F. D. W.: The Effects of Adrenalectomy and Hypophysectomy upon Experimental Diabetes in the Cat, J. Exper. Med. 63:465, 1936.

15. Shipley, R. A., and Long, C. N. H.: Studies on the Ketogenic Activity of the Anterior Pituitary: I. The Relation of Ketonemia to Ketonuria in the Rat; II. A Method for the Assay of the Ketogenic Activity; III. The Nature of the Ketogenic Principle, Biochem. J. 32:2242, 1938.

16. Harrison, H. C., and Long, C. N. H.: Effects of Anterior Pituitary Extracts in the Fasted Rat, Endocrinology 26:971, 1940.

17. Mirsky, A.: The Source of the Blood Acetone Resulting from the Administration of the Ketogenic Principle of the Anterior Hypophysis, Am. J. Physiol. 115:424, 1936.

18. Mirsky, A.; Nelson, N., and Grayman, I.: The Utilization of Acetone Bodies: I. The Influence of Feeding and of Glucose in Nephrectomized Female Rats, J. Biol. Chem. 130:179, 1939.

19. Mirsky, A.: The Site and Mechanism of the Antiketogenic Action of Insulin, Am. J. Physiol. 116:322, 1936.

20. Nelson, N.: The Utilization of Acetone Bodies: III. The Influence of Adrenalectomy, J. Biol. Chem. 132:711, 1940.

21. Somogyi, M.: Changes in Ketonemia and Ketonuria During Hypoglycemia, Proc. Soc. Exper. Biol. & Med. 45:644, 1940.

22. Somogyi, M.: Effects of Insulin upon the Production of Ketone Bodies, J. Biol. Chem. 141:219, 1941.

23. Stadie, W. C.: Intermediary Metabolism in Diabetes Mellitus, Harvey Lect. 37:129, 1941-1942.

24. Leloir, L. F., and Munoz, J. M.: Fatty Acid Oxidation in the Liver, Biochem. J. 33:734, 1939.

25. Lehninger, A. L.: The Relationship of the Adenosine Polyphosphates to Fatty Acid Oxidation in Homogenized Liver Preparations, J. Biol. Chem. 157:363, 1945.

26. Lehninger, A. L.: On the Activation of Fatty Acid Oxidation, J. Biol. Chem. 161:437, 1945.

27. Lehninger, A. L.: A Quantitative Study of the Products of Fatty Acid Oxidation in Liver Suspensions, J. Biol. Chem. 164:291, 1946.

28. Lipmann, F.: Development of the Acetylation Problem, a Personal Account, Science 120: 855, 1954.

29. Lynen, F.: Acetyl Coenzyme A and the Fatty Acid Cycle, Harvey Lect. 48:210, 1953.

30. Ochoa, S.: Enzymatic Mechanisms in the Citric Acid Cycle, Advances Enzymol. 15:183, 1954.

31. Green, D. E.: Oxidation and Synthesis of Fatty Acids in Soluble Enzyme Systems of Animal Tissues, Clin. Chem. 1:53, 1955.

32. Chaikoff, I. L.: Metabolic Blocks in Carbohydrate Metabolism in Diabetes, Harvey Lect. 47: 99, 1953.

33. Stadie, W. C.: Recent Advances in Insulin Research, Diabetes 5:263, 1956.

34. Collip, J. B.: The Occurrence of Ketone Bodies in the Urine of Normal Rabbits in a Condition of Hypoglycemia Following the Administration of Insulin—a Condition of Acute Acidosis Experimentally Produced, J. Biol. Chem. 55:38, 1923.

35. Werk, E. E., Jr.; McPherson, H. T.; Hamrick, L. W., Jr.; Myers, J. D., and Engel, F. L.: Studies on Ketone Metabolism in Man: I. A Method for the Quantitative Estimation of Splanchnic Ketone Production, J. Clin. Invest. 34: 1256, 1955.

36. McPherson, H. T.; Werk, E. E., Jr.; Engel, F. L., and Myers, J. D.: To be published.

37. Engel, M. G., and Engel, F. L.: Influence of Oxycel Corticotropin on Fatty Acid and Glucose Metabolism in the Rat, Endocrinology 58: 808, 1956.

38. Engel, F. L.: Studies on the Nature of the Protein Catabolic Response to Adrenal Cortical Extract: Accentuation by Insulin Hypoglycemia, Endocrinology 45:170, 1949.

39. Bornstein, J.: Insulin-Reversible Inhibition of Glucose Utilization by Serum Lipoprotein Fractions, J. Biol. Chem. 205:513, 1953.

40. Bliss, E. L.; Migeon, C. J.; Eik-Nes, K.; Sandberg, A. A., and Samuels, L. T.: The Effects of Insulin, Histamine, Bacterial Pyrogen, and the Antabuse-Alcohol Reaction upon the Levels of 17-Hydroxycorticosteroids in the Peripheral Blood of Man, Metabolism 3:493, 1954.

41. von Euler, U. S., and Luft, R.: Effect of Insulin on Urinary Excretion of Adrenaline and Noradrenaline: Studies in 10 Healthy Subjects and in 6 Cases of Acromegaly, Metabolism 1:528, 1952.

42. Houssay, B. S.: Diabetes as a Disturbance of Endocrine Equilibrium, Proc. Soc. Biol. Chem. 14:1, 1956.

43. Wool, I. G.; Goldstein, M. S.; Ramey, E. R., and Levine, R.: Role of Epinephrine in the Physiology of Fat Mobilization, Am. J. Physiol. 178:427, 1954.

44. Amatruda, T. A., Jr., and Engel, F. L.: Unpublished observations.

45. Engel, M. G., and Engel, F. L.: Unpublished observations.

46. Warming-Larsen, A.: The Influence of Adrenalin on Blood Sugar and Blood Ketone Bodies in Normal Individuals and in Patients Suffering from Hepatic Disease, Acta med. scandinav. 132:507, 1949.

47. MacKay, E. M.; Wick, A. N., and Barnum, C.: The Influence of Adrenalectomy on the Utilization of Acetone Bodies, Endocrinology 38:30, 1946.

48. Engel, F. L., and Hewson, K.: Fatty Acid and Ketone Metabolism During Hemorrhage and Shock in the Rat, Proc. Soc. Exper. Biol. & Med. 83:608, 1953.

49. Engel, M. G., and Engel, F. L.: Fasting Ketosis in the Adrenalectomized and Cortisone-Treated Rat, Endocrinology 55:593, 1954.

50. Kinsell, L. W.; Margen, S.; Michaels, G. D.; Reiss, R.; Frantz, R., and Carbone, J.: Studies in Fat Metabolism: III. The Effect of ACTH, of Cortisone, and of Other Steroid Compounds upon Fasting-Induced Hyperketonemia and Ketonuria, J. Clin. Invest. 30:1491, 1951.

51. Scott, J. L., Jr., and Engel, F. L.: The Influence of the Adrenal Cortex and Cold Stress on Fasting Ketosis in the Rat, Endocrinology 53:410, 1953.

52. Engel, F. L.; Hewson, K., and Cole, B. T.: Carbohydrate and Ketone Body Metabolism in the Sodium Fluoroacetate-Poisoned Rat: "SFA Diabetes," Am. J. Physiol. 179:325, 1954.

53. Welt, I. D., and Wilhelmi, A. E.: The Effect of Adrenalectomy and of the Adrenocorticotrophic and Growth Hormones on the Synthesis of Fatty Acids, Yale J. Biol. & Med. 23:99, 1950.

54. Gurin, S., and Brady, R. O.: The in Vitro Synthesis of Lipids and Its Hormonal Control, Recent Progr. Hormone Res. 8:571, 1953.

55. Lipsett, M. N., and Moore, F. J.: The Effects of Adrenalectomy and Cortisone Treatment on Fatty Acid Oxidation by Mouse Liver Homogenates, J. Biol. Chem. 197:303, 1952.

56. Perry, W. F., and Bowen, H. F.: Incorporation of Acetate into Fatty Acid by Liver Slices of Adrenalectomized Rats, Am. J. Physiol. 180:21, 1955.

57. Perry, W. F., and Bowen, H. F.: Fatty Acid Utilization by Adrenalectomized Rats, Am. J. Physiol. 186:190, 1956.

58. Welt, I. D.; Stetten, DeW., Jr.; Ingle, D. J., and Morley, E. H.: Effect of Cortisone upon Rates of Glucose Production and Oxidation in the Rat, J. Biol. Chem. 197:57, 1952.

59. Stetten, DeW., Jr.; Welt, I. D.; Ingle, D. J., and Morley, E. H.: Rates of Glucose Production and Oxidation in Normal and Diabetic Rats, J. Biol. Chem. 192:817, 1951.

60. Fajans, S. S., in Proceedings of the Second Clinical ACTH Conference: Vol. I: Research, edited by J. R. Mote, New York, The Blakiston Company, 1951, p. 326.

61. Bennett, L. L.; Kreiss, R. E.; Li, C. H., and Evans, H. M.: Production of Ketosis by the Growth and Adreno-Corticotropic Hormones, Am. J. Physiol. 152:210, 1948.

62. Engel, F. L., and Engel, M. G.: The Influence of Corticotropin on Ketonemia and Glycemia in Normal and Adrenalectomized Rats, Endocrinology 55:845, 1954.

63. Weil, R.: Metabolic Function of the Pituitary Growth Hormone, A. M. A. Arch. Int. Med. 95:739, 1955.

64. Astwood, E. B.: Relation of the Metabolic Effects of Corticotropin Concentrates to Growth Hormone, in International Symposium: The Hypophyseal Growth Hormone, Nature and Actions, edited by R. W. Smith, O. H. Gaebler Jr., and C. N. H. Long, New York, The Blakiston Company, 1955, p. 282.

65. Engel, F. L.: Factors Involved in the Ketogenic Action of Growth Hormone, in International Symposium: The Hypophyseal Growth Hormone, Nature and Actions, edited by R. W. Smith, O. H. Gaebler Jr., and C. N. H. Long, New York, The Blakiston Company, 1955, pp. 344-362.

66. Lotspeich, W. D., and Petersen, V. P.: Effect of Anterior Pituitary Growth Hormone on Synthesis of Acetoacetate by Surviving Slices of Rat Liver, Am. J. Physiol. 176:232, 1954.

67. Petersen, V. P., and Lotspeich, W. D.: Further Aspects of the Endocrine Regulation of Ketogenesis, Am. J. Physiol. 182:273, 1955.

68. Geschwind, I. I.; Li, C. H., and Barnafi, L.: Isolation and Structure of Melanocyte Stimulating Hormone from Porcine Pituitary Glands, J. Am. Chem. Soc. 78:4494, 1956.

69. Tepperman, J., and Tepperman, H. M.: Effects of Cortisone and Purified Pituitary Growth Hormone on Ketogenesis by Surviving Liver Slices, Ann. New York Acad. Sc. 54:707, 1951.

70. Bondy, P. K., and Wilhelmi, A. E.: Effect of Hormones upon the Production of Ketone Bodies by Rat Liver Slices, J. Biol. Chem. 186: 245, 1950.

71. Bahner, F., and Taylor, N. R. W.: Fasting Ketosis in Hypophysectomized and Normal Rats, Quart. J. Exper. Physiol. 37:221, 1952.

72. Greenbaum, A. L., and McLean, P.: The Mobilization of Lipid by Anterior Pituitary Growth Hormone, Biochem. J. 54:407, 1953.

Emergency—Arsine Poisoning

LT. COMDR. W. J. McKINSTRY (MC), U.S.N.R., and J. M. HICKES, M.D., Great Falls, Mont.

Arsine poisoning and metal-fume fever will rarely be encountered by internists who are not industrial physicians. However, in an industrial age, it is possible that some of us will encounter one of them once and will find ourselves in the dilemma described by the authors in which what scant knowledge appears in textbooks is not very useful. It is for this reason that the interesting accounts of their experiences are printed in these pages simultaneously with their appearance in the A. M. A. ARCHIVES OF INDUSTRIAL HEALTH.

PAUL S. RHOADS, M.D.,
Chief Editor

It is our wish in writing this paper that all physicians who see industrial workers at some time in their practice become familiar with the problem of arsine poisoning. True, it is of more importance and interest to the industrial physician. However, any one could have this emergency as his problem at any time. People with an acute illness may bypass the industrial physician and seek aid from the family physician or from one of the specialties. The urologist may be called for the hemoglobinuria, the internist or surgeon because of abdominal pain, etc.

Up to this time, little attempt has been made to present the bits of knowledge to the medical profession except to those whose interests are in the field of industrial medicine or hygiene.

Arsine poisoning is a definite clinical entity. The recognition is relatively simple if one is only cognizant that such a disease process exists. The patient concerned may be exposed to arsine in any one of a dozen or more industrial processes, namely, where arsenic (usually as an impurity) comes in contact with an acid or, as recently shown, with aluminum used in industry as a finely divided dross. In fact, arsine is capable of being evolved in dangerous amounts whenever nascent hydrogen comes in contact with arsenic under certain conditions.

Poisoning from the accidental breathing of arsine still occurs, as we can well attest. Late one afternoon we were advised that four men had become suddenly stricken while at work in a local plant and were being sent to the hospital. A short while later four more men who were possibly exposed were also hospitalized for possible arsine poisoning.

Our failure to find aid from the "common" literature and to be able to read readily available accounts of recent trends of thought regarding treatment has lead us to attempt to place this writing before the physician in a ready reference. It is our hope that our experiences and our search in the literature for purpose of summation of others' past experiences with arsine poisoning (beginning in 1815, when Gehlen, a Munich chemist, died from inhaling the gas in his laboratory) will be of benefit to others.

Our suggestions will be few and are to be considered radical. We profess no great special knowledge except that of the futility of using the present medical treatment, the anxiety of each hour, the steady progression of the symptomatology toward the definite outcome. Once again we report that dimercaprol (Bal) fails to stem the RBC destruction. The oliguria, the anuria, and the uremic state could not be controlled.

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From the U. S. Naval Hospital, Corona, Calif. (Lt. Cmdr. McKinstry), and the North Montana Clinic (Dr. Hickes).

Chemistry and Toxicology

Arsine (hydrogen arsenide, arsenous hydride, arseniuretted hydrogen, AsH_3) is a colorless inflammable gas, which is said to have a strong odor of garlic (most victims state that they smelled nothing unusual at the time of exposure). It is an extremely poisonous gas and is formed whenever nascent H is liberated in the proximity of trivalent As. Its density is greater than air. This toxic gas was first described by Scheele, who identified it in 1775.

The most serious type of arsenical poisoning is that caused by arsine. Arsine exerts its effects on the hemoglobin of the RBC, causing hemolysis, hemoglobinuria, and jaundice. Actually, arsine is probably the only powerful hemolytic agent found in industry.

Nau [7] has reported that the main factors concerned with the lethal action of arsine are (1) hemolysis of the RBC's with the liberation of toxic arsenical compounds; (2) the blocking of the renal tubules by the products of the Hb. breakdown, giving rise to oliguria, anuria, and uremia, and (3) the resulting decreased O_2-carrying capacity of the blood. Hemoglobin is said to be the only constituent of blood that will react vigorously with arsine, and arsine is fixed in the blood in a nonvolatile form. The fixed arsenic is largely confined to the erythrocyte up to the time of hemolysis.

Even though the gas apparently is readily soluble in the blood plasma and the resulting rapid fragmentation of the RBC's is great, there is some arsine that escapes fixation by the RBC to be carried to the vital organs. Almost all of the toxic effects can be explained by the RBC destruction, but the damaging effect on the tissues of the liver, spleen, kidneys, lungs, etc. is also direct and severe. In massive dosages the destruction of the blood can be almost complete, and its importance far overshadows the other toxic effects.

It has been estimated that 0.10-0.15 gm. is a single fatal dose of arsenic for man.

Air containing 50 ppm of arsine is usually considered dangerous, and 30 ppm will produce symptoms of poisoning after several hours. As little as 16-60 ppm is said to produce serious symptoms after one hour of exposure, and one-half hour of 250 ppm will usually produce death. The American Conference of Governmental Hygienists has set the figure of 0.05 ppm as the maximum safe concentration for prolonged exposure.

Arsine Poisoning in Industry

Poisoning from arsine in industry is not as isolated as one might at first imagine. In 1928, Muehlberger, Loevenhart, and O'Malley listed 215 cases occurring since 1815, of which 20% were fatal. Spolyar and Hager, in their review of the literature, found 30 cases with 12 deaths that were reported in the period from 1923 to 1941. Spolyar and others reported on 21 cases with 4 deaths in 1950. There doubtless have been unrecognized cases, and when those cases which have never been reported are added we must realize the importance of this potent industrial hemolytic agent.

The highest incidence of arsine poisoning has been in the metallurgic industries, the vast majority of these cases being due to the action of acid on arsenic-bearing metal. There have been cases due to the evolution of arsine from the wetting of aluminum dross and in the tin industry. Bulmer et al. have reported on 14 cases that occurred in Canada and this country in workers who were recovering gold and silver with the MacArthur-Forrest process. Others have reported poisoning in the process of leaching zinc and other metals. Wills reported death of a man cleaning out a steel furnace containing a calcium arsenide and phosphate dross. Later, cases were reported by Spolyar and Hager and also Nau of arsine poisoning due to the use of aluminum for removal of arsenic and antimony in the refining of lead. Other cases have been reported from ferrosilicon and refining of tin. Our cases resulted from the action of acids during the leaching process in a purification residue

department of an electrolytic zinc plant, which, incidentally, has been carried on for some 40 years under accepted safety precautions.

Arsenic, then, can be a contaminant in many of the recoverable ores of industry—zinc, lead, copper, antimony, gold, silver, tin, and others. It can also be an impurity in the manufacture of hydrochloric acid. Arsine poisoning has also been reported in storage-battery manufacture and in the cleaning and repairing of tanks used in industry where arsenic has been a contaminant during the processing of various chemicals or metals. Of course the manufacture of arsenicals themselves, under the proper conditions, could be a source of this gas.

In many industries arsine is an ever-ready ominous "uninvited guest"—much like Longfellow's "famine and fever."

In all cases of mysterious illness among workers with metals and/or acids a search for the possibility of arsenic and arsine should be made. As seen above, the H^+ ion need not be furnished by an acid, but it is possible to form arsine in the presence of arsenic if hydrolysis (or perhaps electrolysis) is permitted to occur where aluminum dross is wetted in metallurgy.

It is imperative that an "industrial history" be taken and included in the patient's personal history. This habit may prove helpful not only to discover probable arsine poisoning but also in diagnosing other causative industrial toxins as well.

Industry has an important role in providing (1) knowledge that the gas is capable of being produced with any given process, (2) modern, adequate means of detection and reliable warning devices should arsine be liberated within the working areas, (3) efficient ventilation mechanisms in areas where arsine might be liberated, and (4) education of the workers and other responsible parties to the dangers of the gas and the importance of strict controls as above.

The "ounce of prevention is worth a pound of cure" adage is of the most importance in the treatment of arsine poisoning. It is an important part of a safety program in many industries.

Case Studies

Our cases, which include eight workers exposed to arsine, are not unique in symptomatology, course, or final outcome. Persons who have had a lethal dose die. The symptoms presented by the four men who did not survive were classical to the physician who has seen or read about arsine poisoning. The other four men, who were minimally exposed, presented no significant findings on admission nor during the 24-hour observation period. Follow-up studies showed no evidence of poisoning. Unfortunately, no ECG studies were made on any of these men.

At approximately 4:45 p. m. on a cooling, waning September afternoon in 1950, a call was received at the North Montana Clinic informing us that four men were acutely and severely ill and were being transferred to the hospital via the company ambulance. Arsine poisoning was suspected, but the silver nitrate trains did not show arsine to be present in the area where the men had been working. Two of us met the patients at the hospital, where the following story was unfolded.

On Sept. 9, 1950, at approximately 4 p. m., four men were working on a routine job in the purification residue plant at a chemical processing vat. The vat was said to be located in an enclosure open to the outside air on three sides. It was stated that one man complained of a pain in the abdomen and feeling of nausea. He went to another part of the building for approximately seven or eight minutes, then rejoined his fellow workers. By this time all four complained of some abdominal pain and nausea, some dizziness or giddiness, and numbness in the face and hands. When questioned later two of the men said they had smelled nothing. The third said he noticed an odor resembling decaying or burning horseflesh. The fourth said there appeared to be a smell of garlic or onions.

TABLE 1.—*Survival Time After Exposure*

Case	Age	Admission	Death	Survival Time
1	25	9/9/50	9/11/50	53 hr.
2	20	9/9/50	9/16/50	7 days
3	48	9/9/50	9/17/50	8 days
4	20	9/9/50	9/23/50	14 days

Altogether there was a probability of exposure to a noxious gas for 15 to 20 minutes, when it was suggested by others that they should go to the hospital. They were brought to the hospital and admitted at approximately 5 p. m., all having fairly similar complaints and showing comparable symptoms.

The four patients who died showed a rather similar course, but their deaths varied from the first to die, within some 50 hours after exposure, to the fourth fatality, occurring 12 days later. The other four men who were later admitted were dismissed from the hospital after 24 hours of observation and were followed as outpatients without evidence of acute arsine poisoning. These last four are not included in this study. Chronic arsine poisoning has been reported, but we are here concerned with the emergency existing in the case of acute exposure only.

Symptoms and Complaints.—All of the four who died complained of severe nausea upon admission and had numerous emeses. Headache was complained of by all four, and in two it was severe. Abdominal pain, cramping in nature, was present in the four patients and was extremely severe in one (Case 1), who also had bilateral costovertebral pain, as well as bright red blood mixed in with the bile-colored emesis. Only one patient voided voluntarily after the initial urine specimen collected in the emergency room. Two (Cases 2 and 4) voided clear amber urine; the other two passed dark red urine when the first specimen was collected. Within 12 hours all had marked hemoglobinuria. Three of the four complained of numbness and tingling of the hands, feet, and face at the time of admission. Case 1 appeared to be in the greatest distress and was the first to die. All presented fear facies and appeared to have the knowledge of impending disaster (Table 2).

Physical Findings.—In Table 3 one can see a fairly comparable trend in the recording of temperature, B. P., pulse, and respirations during the first six-hour period. The physical findings were far from striking except for early abdominal tenderness, with board-like quality of the abdominal muscles. The tenderness was present in three of the four and the abdominal rigidity was present in two at the time of admission. There was early evidence of pulmonary edema in Case 1. Other than the rapid apical beats, rales, and decreased breath sounds in Case 1, the examination of the chest was negative. Actually, except for the above and a moderate amount of facial edema in Case 1 within the first 24 hours, the examinations were otherwise of little clinical importance. Icteric sclerae were observed within 48 hours in one patient (Case 1). All patients were observed not only to have the brownish-yellow discoloration of the sclerae before death but to have a deepening jaundice of

TABLE 2.—*Symptoms and Complaints—Listed by Severity*

	Case 1		Case 2		Case 3		Case 4	
	Admis.	24 Hr.*	Admis.	24 Hr.	Admis.	24 Hr.	Admis.	24 Hr.
Nausea and vomiting	+++	+++	+	+++	+++	+++	++	+++
Headache	+++	++	+	+	+++	++	++	+
Abdominal pain	+++	+++	+	+	++	+	+	+
Numbness	++	++	0	+	++	0	+	0
Vertigo	+++	+	0	0	++	0	0	0
Restlessness	++	+++	0	+	0	++	0	++
Muscle twitch	++	+++	0	+	0	+	0	+
Cough	++	++	++	+	+	+	+	+
Singultus	++	+	0	0	+	0	++	+
Distention	++	++	0	++	0	0	0	+
Kidney pain	++	+	0	0	0	0	0	0
Muscle aching	+	+	0	0	0	+	0	0

* 24 hours or later.

TABLE 3.—*Physical Findings*

	Temp., F	B.P.	Pulse	Resp.
Admission, 5 p.m., 9/9/50				
Case 1	103	162/95	126	"Rapid"
Case 2	102	120/90	60	32
Case 3	98.8	145/110	84	20
Case 4	99	130/90	92	28
11 p.m., 9/9/50				
Case 1	102.8	126/80	124	"Rapid"
Case 2	102.6	128/80	82	24
Case 3	101.4	112/82	92	24
Case 4	102.2	144/66	104	--

the skin, noted beginning within the first 48 hours. Conjunctival and mucosal injection was noted in all patients upon admission.

As each patient approached death the usual findings associated with a uremic death were observed.

Case 1 was admitted to the hospital at 5:00 p. m. Sept. 9, 1950; taken to ward by wheel chair. B. P., 162/95.

5:20 p. m.: Salt water was given as emetic.

6:00 p. m.: Patient vomited thick green fluid and a small amount of blood. Appeared cyanotic, was sweating profusely, complaining of pain in the kidney region. Vomited thick greenish fluid and bright red blood frequently. Coughed a great deal.

Sept. 10, 1950, 1:50 a. m.: The skin had a very red appearance.

3:30 a. m.: Unable to void. Catheterized. Urine had a dark, bloody appearance. Coughing a great deal and vomiting bright frothy blood frequently.

3:45 a. m.: B. P., 100/80. Restless and in pain in spite of sedation with morphine. Dark bloody urine obtained per catheter.

10:00 a. m.: Abdomen distended. Coarse rales heard throughout chest. Patient in much distress. Breathing with difficulty. Oxygen tent—color remained dusky.

Sept. 11, 1950, 12:10 a. m.: Did not appear to respond well. Patient very restless. Coughing continuously. Skin very red. Frequent vomiting of bloody, frothy material continued.

1:00 a. m.: Very marked muscular twitching.

2:30 a. m.: Skin clammy, extremities cyanosed.

8:00 a. m.: Complained of abdominal pain. Became rigid when arm was disturbed.

2:30 p. m.: Extremely restless, profuse sweating. From this time patient's condition deteriorated rapidly until death, at 9:25 p. m.

Laboratory Findings.—On admission Case 1 already showed severe anemia, with 3,000,000 RBC and a Hb. of 9.4 gm., or 59%. It is interesting to note that Case 4, who survived 14 days, had the second worst blood picture upon admission (3,250,000, with 10.8 gm., or 67.5%). It was possible to keep all patients' blood up to around the 4,000,000 level, except for Case 1, whose anemia progressed in spite of adequate transfusion.

In our cases, as reported by others, a leukocytosis was present early in the course of the disease. The highest count reported was that of Case 1, on the morning of the second day, with 34,000 WBC, including 85% polymorphonuclear leukocytes and 12% lymphocytes. Case 4 showed a white cell count of 22,000 and a differential of 80% polymorphonuclear leukocytes and 15% lymphocytes.

At the present the basis of the leukocytosis is unexplainable. CO_2 volumes determined within eight hours after admission were reported as being within normal limits. Blood calcium levels were raised to as high as 21.5 mg. per 100 cc. (normal, 9-11 mg. per 100 cc.) by the third day.

Urea nitrogen determinations done at regular intervals showed an increasing uremic state, and abnormally high values were obtained in all four patients by the end of 48 hours.

Urinalyses were done whenever specimens could be obtained. Three of the four showed a positive benzidine test for occult blood in the urine upon admission. Two of the four passed clear urine as the initial specimen, the other two passing wine-colored urine at this time. As would be suspected, positive tests for albumin were reported on those specimens showing a positive benzidine reaction. Within 24 hours all patients had clinically evident hemoglobinuria. All urines were alkaline after the first 24 hours. After 12 hours specimens were almost nil, with only three spontaneous voidings being recorded. Specimens obtained via catheter were meager in amount. During the second hospital day one patient (Case 2) was reported to have a total urinary output of some 150 cc. This was the most recorded for any patient. The total amount of urine recorded for the four men was 1850 cc., of which over 800 cc. was collected during the first 12 hours.

(This total was over a period of 31 man-hospital days.)

In one early specimen 100 RBC per high-power field was reported. Other than this, no significant microscopic findings were reported.

Treatment.—Emergency treatment consisted of the use of morphine or meperidine (Demerol) for the relief of pain and anxiety, warmth and position for impending shock, and the early administration of intravenous fluids while typing and cross matchings were being done. Oxygen was used in an attempt to relieve the nausea and apparent air hunger. It was decided to administer dimercaprol, and the first injections were given within two hours following the supposed initial exposure time.

Dimercaprol was given in dosages up to 2 cc. every four hours. This amounted to 0.5 cc/45 lb. of body weight. Our local supplies, we knew, would soon be exhausted. However, thanks to the U. S. Air Force, our supplies were soon replenished from the East. One patient, Case 4, received 1.7 cc. q. 4 h. for 10 doses and then b. i. d. for three days. Case 2 developed a mild pruritis on the fifth day, but we did not believe it to be a side-reaction of the dimercaprol.

Whole blood and packed RBC were used copiously to combat the effects of the RBC destruction. In all, over 30 pt. of whole blood and 18 units of packed RBC were used.

Other supportive measures, such as electrolytes, vitamins, and calories were given parenterally.

Total fluid intake was regulated to between 3000 and 4500 cc. daily, given as blood, isotonic saline, and 5% or 10% dextrose. The amount of saline was regulated by the amount of recorded emesis.

Morphine and meperidine were used as needed to control pain and anxiety.

Results.—The inhalation of arsine, which occurred over an estimated period not exceeding 20 minutes, proved a formidable opponent, and the fight for survival proved futile, with a fatal outcome for the four men.

Conclusions and Comment

Almost 7 years have passed since this catastrophic emergency, happening during a routine process that had been in progress for almost half a century. Much thought and preparation has accumulated in these six years.

Arsine, when inhaled in concentrations above the safe level, causes a serious emergency that happens infrequently. In our community not only was one group of physicians involved (those of us who were directly responsible for their care), but many other physicians consulted with us during the care of these men. The internist, the urologist, the general practitioner, the pathologist, and others were concerned. We were all appalled at the lack of our collective knowledge.

Dimercaprol has been suggested, and used, in the treatment of arsine poisoning. Its value has not been proven in the past, and we, in our series of cases, feel that it did not stem the red blood cell destruction or otherwise alter the course of these four patients. Administration of the drug was begun approximately two hours after exposure. We felt that the dosage was adequate.

Other chelating agents have been introduced in the past few years, and one, edathamil calcium-disodium (Calcium Disodium Versenate) has been proven to be of real value in the treatment of lead poisoning and has a probable place in the treatment of other heavy-metal poisonings. Preliminary trials of edathamil calcium-disodium have not merited further study in the treatment of arsenical poisoning. Perhaps further investigation along these lines will bring a more promising drug in the future.

The question of a method of approach should one be confronted with this problem is still, in our minds, a rather moot question. Because, in the final analysis, the hemoglobinuria causes tubule blockage and ensuing uremia, this problem must be solved to prevent a fatal outcome.

Massive exchange transfusion offers us a possible method of (1) reduction of the

circulating reduced hemoglobin and red blood cell debris, thus preventing tubule blockage; (2) reducing the arsenic and arsenical compounds in the circulating blood. It has not been attempted, as far as we know, but in the light of the absence of other effective methods of control it is proposed for a new approach to this problem. The many difficulties that would have to be overcome are fully appreciated, and we realize that blood supply, typing, and cross matching would prove a formidable problem. Cases should be carefully selected, because we know that those receiving less than lethal dosages will recover without apparent sequellae. However, the patient receiving a lethal dose is doomed, and his fate is sealed at a very early hour. Therefore, haste in selection and beginning the procedure is paramount. Here procrastination—even for an hour—will prove to be disastrous. If symptoms of very severe poisoning were to be seen again by us, we have agreed to begin the exchange transfusion as soon as the diagnosis is made. The radicalness in this approach is recognized, and apologies are asked for our suggesting this as-yet-untried method.

The true solution, of course, resolves itself about the first step in the treatment of any disease process—prevention. Adequate ventilation, education, and efficient warning devices are essential in any industry where arsine gas is a possibility. The odor of the gas definitely cannot be relied upon for its detection.

Morse and Setterlind[5] state: "Despite the fact that arsenic is a long known impurity of many metals, arsine poisoning has been given relatively scant attention by members of the profession of industrial medicine and hygiene. Many cases have been reported in medical literature, however, and any student of the problem is soon acquainted with what appears to be a paradox, namely, poisonings by a potent hemolytic agent and comparatively little sustained effort being made by the members of the industry and the professions most directly concerned with investigation and control."

Be this so, if the emergency arises it is still the responsibility of the physician or physicians concerned to prevent suffering and preserve life.

Morse and Setterlind report a case in which the diagnosis of arsine poisoning was not made by the family physician, although this patient presented the cardinal symptoms, with abdominal cramps, nausea and vomiting, generalized pains, and anuria from the first day of illness (exposure day). On the fourth day he was hospitalized, with an RBC of 1,500,000 and Hb., 51%.

Pinto et al. feel that characteristic ECG changes were present in all of their cases—even those minimally exposed, and they feel that it is the most sensitive test available for the diagnosis of arsine poisoning.

Most other investigators have found a longer latent period between exposure and onset of symptoms; however, gas concentrations must be taken into consideration as to the timing of findings following exposure.

In our series of cases two autopsies were permitted and were performed by Dr. J. T. Fallon, then pathologist at Columbus Hospital, Great Falls, Mont. A summary of one protocol is included at the end of this paper for those who may be interested in the pathologic findings. Some tissue arsenic determinations were done on one patient, and the following analysis, calculated as elemental As in 50 gm. of tissue, was reported by Alexander O. Gettler, Ph.D., Professor of Toxicology, New York University College of Medicine: kidney, 0.20 mg.; liver, 0.28 mg.; blood, 0.15 mg.

Those interested can find further sample determinations of various tissues in an excellent article by Garlick.[3]

For convenience, the diagnosis and differential diagnosis are summarized in Table 4.

Summary

Arsine poisoning is an infrequent emergency, calling for heroic and immediate measures if the hemolytic and toxic effects of this gas are even hoped to be overcome.

TABLE 4.—*Diagnosis and Differential Diagnosis*

Diagnosis
1. Nausea and vomiting
2. Abdominal pain
3. Numbness
4. Headache
5. Vertigo
6. Hemoglobinuria
7. Oliguria and anuria
8. May be shock picture
9. History of industrial worker (most likely in metallurgy)
10. Positive benzidine test (urine)
11. Anemia
12. Leukocytosis
13. ECG changes
14. Fever
Differential Diagnosis
1. Paroxysmal hemoglobinuria
2. Weil's disease
3. Potassium chlorate poisoning
4. Pyrogallic acid poisoning
5. Blackwater fever
6. Mixed industrial poisoning

Arsine is capable of being evolved whenever contaminated ores containing arsenic come in contact either with a hydrogen ion from the action of acid on metal or with aluminum used as a finely divided wetted dross (which probably evolves hydrogen by electrolysis or hydrolysis). Professor Drinker points out that arsine can be generated in dangerous amounts when moisture from the air reacts with metallic sulfides containing small amounts of arsenic. All that is needed is nascent hydrogen and arsenic under certain conditions. Most cases have been reported in the meallurgic industries.

Eight cases are here added to the medical literature, four cases having been probable exposures without presenting valid symptoms or definite findings. The other four, who presented severe symptoms and complaints upon admission, died between the 3d and the 14th days.

Dimercaprol was considered to be of no benefit. Early exchange transfusion is advocated as a possible method of approach to this problem until some other less radical form of treatment has proven to be effective.

The importance of the part industry and other responsible agencies must play in prevention is stressed.

In sublethal dosages, complete recovery is apparently the rule. ECG changes, as described by others, are felt to be of importance in the diagnoses of even minimal exposure cases.

Synopsis of Autopsy Protocol of Case 1

The body is that of a well-developed and well-nourished adult white man, 25 years old, measuring 5 ft. 7 in. in height and weighing 136 lb. There is a dusky, deep-brownish discoloration of the skin and mucous membranes of the entire body. Rigor mortis is present in slight degree.

Head.—The only finding of note is the brownish-yellow color of the sclerae.

Body.—The fat is slightly brownish-tinted yellow in color. The muscles are deep beefy red in color.

Peritoneal Cavity.—Essentially negative.

Pleural Cavities.—The left pleural cavity contains approximately 500 cc. of dark fluid blood.

Pericardial Cavity.—The pericardial cavity contains about 20 cc. of dark, amber-colored fluid.

Heart.—Weight, 410 gm. The epicardium is smooth and glistening. There are a number of small subepicardial extravasations of blood.

Lungs.—Right, 760 gm.; left, 630 gm. Both lungs are similar. They are heavy and wet, containing considerable amounts of air. Fine, soft, boggy nodulations are felt throughout the parenchyma of both lungs. On section there is a course, slightly brownish-to-red soft nodulation on a spongy deep-purplish-red parenchyma. The lighter nodulation surrounds bronchioles. Very large amounts of dark blood-stained froth are expressed from the cut surfaces. Small droplets of thin blood-stained mucoid material are expressed from the cut ends of the bronchioles. The bronchi and trachea contain large amounts of dark blood-stained froth. The epithelial linings of the bronchi and trachea are swollen, congested, and edematous.

Spleen.—Weight, 250 gm. The capsule is smooth and tense, with a fine irregular dark-reddish mottling. On section the cut surfaces are deep, dark purplish-red. A large amount of pulp is scraped away.

Liver.—Weight, 690 gm. The capsule is smooth and tense. The liver is light brownish. On section the cut surfaces are light, strictly tinged greenish brown, with a fine purplish mottling. The cut surfaces are wet and greasy.

Pancreas.—Weight, 150 gm. The pancreas is unusually soft.

Gastrointestinal Tract.—The stomach is moderately dilated and filled with very dark greenish-brown, almost black fluid material containing fine black coffee-ground-like material. The subserosal blood vessels are fairly markedly conjested. The mucosa is greenish stained, with numerous small, dark-red, submucosal hemorrhagic foci.

The entire gastrointestinal tract is somewhat distended and filled with material similar to that described in the stomach. There is a light green-

ish-brown discoloration of the bowel wall, except in one area about 30 cm. in length in the midportion of the ileum, where the bowel wall is deep dark-reddish and remarkably soft. The entire mucosa has a congested, edematous appearance, with numerous small mucosal dark hemorrhagic areas in different portions; with enough dilution the material in the entire gastrointestinal tract is brownish green.

Adrenals.—Normal in size. The adrenals are soft, congested, and remarkably friable.

Kidneys.—Left, 250 gm.; right, 250 gm. The kidneys are similar. The capsules are remarkably tense. The kidneys are practically black, with a bluish-green sheen of the capsules. On section the cut surfaces are somewhat elevated above the cut edges of the capsules. The surface is swollen and edematous in appearance. They are almost black. The cortices measure 0.1 cm. in thickness. The junction between cortices and pyramids is almost indistinguishable. The cut surfaces are fairly markedly congested.

Comment.—The spilled blood is very dark brownish red. Wiping it from a white surface leaves a greenish-yellow stain. The fascia, cartilages, and tendons show a light greenish-brown tinting.

Microscopic Examination.—Heart: The epicardium is not remarkable. In the myocardium there is a generalized cloudy swelling of the sarcolemma of the muscle fibers which is early and of moderate degree, varying to some extent in different areas. There is a moderate degree of fragmentation of the muscle fibers in different areas. The nuclei of large numbers of the muscle fibers are unusually large, pale, and vacuolated. Many of the venules contain clumps of degenerating red blood cells which are separated and surrounded by deposits of hemosiderin. The endothelial cells lining these blood channels are severely swollen, with acidophilic-staining cytoplasm and poorly defined lymph-cell membranes.

Lungs: The alveolar spaces throughout all sections of lung tissue taken contain very numerous, remarkably large alveolar phagocytes. Some of these phagocytes are giant in type, with a single nucleus. Others contain 2 to 10 nuclei. The cytoplasms of these alveolar phagocytes contain combinations of anthracotic pigment, hemosiderin, hemoglobin, ingested red cells, and clear vacuoles. Practically every alveolar space contains some normal-appearing red blood cells. Much cellular debris is encountered within the alveolar spaces. Some alveolar spaces contain masses of greenish-yellow- to deep-brownish-colored finely reticulated material. There is a generalized swelling, with marked edema of the endothelial cells lining the alveolar spaces and alveolar sinusoids. Small ruptured areas are seen in the walls of large numbers of the alveolar sinusoids. Many of the bronchioles are plugged with alveolar phagocytes, red blood cells, serum, and desquamated epithelial cells. The lining epithelium is swollen and edematous and is breaking away from the walls in different areas. The peribronchiole connective tissues, lobar septa, and subpleural connective tissues are very markedly edematous, with stretching and breaking apart of connective tissues. The lymphatics in these regions are very dilated and are filled with serum. Most of the branches of the pulmonary veins contain only serum without cells. The lymphatic aggregations of the lung tissue are enlarged and edematous. Numerous small areas of interstitial hemorrhage are seen in the subpleural regions.

Spleen: The lymphoid elements are large and numerous. They contain considerable numbers of eosinophils. Most of them show proliferations of their germinal centers. A picture which simulates amyloid disease is seen in a considerable number of the germinal centers. There is a moderate degree of proliferations of the reticuloendothelium. The reticuloendothelial cells are greatly swollen and edematous. Phagocytosed red blood cells and hemosiderin are seen in many of the reticuloendothelial cells. The sinusoids are dilated and swollen, as are the blood vessels. The trabeculae and the walls of many of the blood vessels show a generalized greenish brown staining. The capsule is not remarkable.

Pancreas: The islet and acinar tissues are not unusual except that considerable numbers of hyperchromatic nuclei and frequent mitotic figures are seen in the acinar cells. Numbers of the ducts are dilated and filled with inspissated secretion. The interstitial tissues and blood vessels are not remarkable. The pancreas is well preserved and stained.

Gastrointestinal Tract: Sections of the walls of the gastrointestinal tract taken from a number of areas all show similar histopathological changes. There is slight generalized edema of the mucosa, with desquamation of the superficial layers of the mucosa. The blood vessels throughout the wall are markedly dilated and congested. The lumen contains desquamated epithelium and brownish, finely particulate material similar to hemosiderin.

Liver: There is a marked generalized cloudy swelling of the cytoplasm of the liver cells, especially in the midzones of the lobules. The intercellular sinusoids are dilated and filled with serum and granular cellular debris. The blood vessels are dilated and congested. Glisson's capsule and the biliary ducts are not remarkable.

Adrenals: Both adrenal glands show identical histopathologic changes. They show evidences of excessive secretory activity. These cells of all layers are markedly swollen. The cells of the zones of Lucita are extremely pale. In a number

of areas they are in acinar formations, forming lumina which are filled with deeply acidophilic material similar to the colloid of the thyroid gland. The intercellular sinusoids and blood vessels are markedly dilated and congested. The cells of the medullae are swollen. The cytoplasm is remarkably clear, finely granular in some of the cells. The adrenal glands are not otherwise remarkable.

Kidneys: Both kidneys show similar histopathologic changes. The cells of the glomerular tufts are swollen and edematous, disintegrating in some areas. Many of the glomerular spaces are filled with red blood cells and serum. There is a diffuse cloudy swelling, with granularity of the tubule cell cytoplasm. The proximal convoluted tubules and descending portions of the loops of Henle are filled with red blood cells and debris of red blood cells. Small portions of their debris are being picked up by the tubule cells in these regions. The ascending portions of the loops are filled with dense casts of deeply reddish-brown-staining wax-like material which is a cellular and appears to have a high hemoglobin content. The interstitial tissues and blood vessels are not unusual.

U. S. Naval Hospital, Corona, Calif.

REFERENCES

1. Belknap, E. L.: EDTA in the Treatment of Lead Poisoning, Indust. Med. 21:305 (June) 1952.

2. Bulmer, F. M. R.; Rothwell, H. E.; Polack, S. S., and Stewart, D. W.: Chronic Arsine Poisoning Among Workers Employed in the Cyanide Extraction of Gold: Report of 14 Cases, J. Indust. Hyg. & Toxicol. 22:111 (April) 1940.

3. Garlick, H. W.: A Case of Industrial Poisoning with Arsine Treated with British Anti-Lewisite, M. J. Australia 1:69 (Jan. 15) 1949.

4. Gonzales, T. A.; Vance, M.; Helpern, M., and Umberger, C. J.: Legal Medicine: Pathology and Toxicology, Ed. 2, New York, Appleton-Century-Crofts, Inc., 1954, pp. 743, 894-895.

5. Morse, K. M., and Setterlind, A. N.: Arsine Poisoning in the Smelting and Refining Industry, Arch. Indust. Hyg. 2:148 (Aug.) 1950.

6. Muehlberger, C. W.; Loevenhart, A. S., and O'Malley, T. S.: Arsine Intoxication: A Case of Suspected Poisoning in the Steel Industry, J. Indust. Hyg. & Toxicol. 10:137 (May) 1928.

7. Nau, C. A.: Accidental Generation of Arsine Gas in Industry, South. M. J. 41:341 (April) 1948.

8. Pinto, S. S.; Petronella, S. J.; Johns, D. R., and Arnold, M. F.: Arsine Poisoning: Study of 13 Cases, Arch. Indust. Hyg. 1:437 (April) 1950.

9. Spolyar, L. W., and Hager, R. N.: Arsine Poisoning: Epidemiologic Studies of an Outbreak Following Exposure to Gases from Metallic Dross, Arch. Indust. Hyg. 1:419 (April) 1950.

10. Steel, M., and Feltham, D. V. G.: Arsine Poisoning in Industry: Report of Case, Lancet 1:108 (Jan. 21) 1950.

11. Thompson, J.: Personal communication to the authors, Riker Laboratories, Inc.

12. Wade, J. F., Jr., and Burnum, J. F.: Treatment of Acute and Chronic Lead Poisoning with Disodium Calcium Versenate, Ann. Int. Med. 42: 251 (Feb.) 1955.

13. Wills, R. A.: Arsine Gas Poisoning—Report of a Case, Indust. Med. 17:208 (June) 1948.

Metal-Fume Fever from Inhaling Zinc Oxide

LT. COMDR. LLOYD C. ROHRS (MC), U.S.N.

Metal-fume fever is an acute industrial illness which follows the inhalation of finely dispersed particulate matter formed when certain metals are volatilized. The oxides of the following metals are capable of causing the disease: antimony, arsenic, cadmium, cobalt, copper, iron, lead, magnesium, manganese, mercury, nickel, tin, and zinc.[1-5] When zinc or one of its alloys is burned, melted, or heated in air to greater than 930 F, the oxide is formed as a fine dispersion of dry particles of about 1μ in size. The inhalation of these causes a common, transient, benign form of metal-fume fever. In the past this disease has been called "brass founder's ague," "zinc fever," "zinc chills," "Spelter's shakes," "glavo," and "metal shakes."[1,4] Industrial workers in recent years who perform bronzing, galvanizing, copper rolling, or welding of zinc or galvanized iron have experienced symptoms of this disease.[1]

Symptomatology

During exposure to the fumes of zinc oxide, dryness and irritation in the throat and a sweetish taste in the mouth are initially experienced. The dryness of the throat increases, becoming associated with substernal tightness, constriction in the chest, and development of a dry cough. Several hours following exposure lassitude, malaise, fatigue, frontal headache, low back pain, cramps in the muscles, and occasionally blurred vision are noted. Chilly sensations, shivering, and trembling appear. If the person is exposed to a cool environment, a malaria-like chill at times is experienced which may last several hours, followed by myalgia. Nausea and occasionally vomiting occur. When examined the patient has fever, perspiration, dyspnea, rales throughout the chest, and tachycardia. There is a polymorphonuclear leukocytosis. The roentgenogram of the chest is invariably normal or reveals only increased bronchovascular markings. Such an attack may last from 6 to 12 and rarely 24 hours. Weakness and mild prostration follow, but recovery is complete. With repeated exposure an increased tolerance develops and a seeming immunity is acquired. The "immunity" is quickly lost during holidays or over a weekend, for the attacks are observed to be more frequent and more prevalent on Monday.[2-4]

Report of Cases

CASE 1.—A 42-year-old white male welder was in good health on March 12, 1955, when he began his usual occupation of arc welding on galvanized iron pipes. Two blowers were used to ventilate the area. Ordinarily the men performing this task were rotated frequently, but because the job was done on a weekend the patient had to work from 8 a. m. until 2 p. m., except for a short lunch period. While welding he gradually developed a slight metallic taste in the mouth and bitemporal headache. Gradually, as the exposure to the fumes continued, he experienced the onset of shaking and shivering, with chilly sensations. He noted a feeling of fever, nausea, and a dry, harsh cough with associated dyspnea. Cramps in the muscles were attributed to the severe shaking. When first seen at his place of work he was very dyspneic but not cyanotic. The temperature was 103 F orally. He was given oxygen for about 15 minutes and rushed to the hospital. Upon admission he gave a history of having had many similar episodes in the past and, despite the discomfort, was somewhat annoyed at having been rushed to the hospital as an emergency. He had had like symptoms in the past after welding galvanized iron and had seen them in other welders. Sputum was rarely produced in

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From the Medical Service, U. S. Naval Hospital, Oakland, Calif.

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spite of the cough. He volunteered that with severe episodes vomiting would occur. He knew that the degree of illness was proportional to the length of exposure to the fumes and that it usually took several hours before the symptoms began. The patient was most emphatic in stating that the symptoms would be alleviated within an hour or two by taking milk and cream or olive oil. He stated that other welders, as well as himself, frequently would drink rich milk before welding on galvanized iron, in an attempt to avert the illness.

The physical examination revealed a well-developed, large, muscular person. He was minimally dyspneic and shaking. He had a hoarse, raucous, nonproductive cough. He was perspiring freely. The temperature was 103.4 F orally. There was a tachycardia of 112. Coarse breath sounds, rales, and wheezes were heard throughout the entire chest. The examination revealed no other pertinent abnormalities. The white blood cell count was 21,300, with a differential of 82% polymorphonuclear leukocytes and 18% lymphocytes. A roentgenogram of the chest was within the limits of normal.

As the patient had requested, he was given milk liberally and was observed in the emergency room. Over the ensuing two to three hours the fever gradually subsided, dyspnea and chills disappeared, and the auscultatory findings in the chest became normal. The improvement after three hours was so striking that, at his insistence, he was not hospitalized but was sent home. The total period of observation was about five hours. He was at work the following Monday.

Although this disease is common in welders, reports have not been found of persons using buffing machines on zinc-coated surfaces who have developed the typical symptom-complex. Two men were independently employed cleaning potable water tanks of ships in dry dock. These tanks have an inside coating made of a zinc dust preparation. Removal of this ordinarily is done by sandblasting. Occasionally a rotatory steel wire automatic brush is used. Heat and dust are created during the process. The following two cases illustrate an unusual means by which metal-fume fever was contracted and the error which initially arose in diagnosis.

CASE 2.—An 18-year-old white youth was admitted to the U. S. Naval Hospital, Oakland, Calif., on June 25, 1956, with a diagnosis of infectious mononucleosis because of intermittent chills and fever for the previous three weeks. The man was employed in the capacity of cleaning the potable fresh water tanks, using a rotating-wire automatic buffing machine. Considerable dust and particulate matter were produced by this procedure, and the machine became very hot. A mask to diminish inhalation of dust was worn. The first day he was employed in this capacity he experienced the onset of malaise, chills, fever, cough, and subsequently nausea and vomiting. These symptoms recurred periodically with such regularity that he soon associated them with the daily descent into the tank for buffing. They usually were not experienced until the end of the day, and frequently the man would not observe them until he went home in the evening. On June 25, 1956, a Monday, he reported to work in his usual state of good health. In the afternoon he had a particularly severe episode of chills and fever, with shaking of the entire body. He noted a cough productive of frothy sputum and intense nausea with one episode of vomiting. As he was still on duty he was taken to the local dispensary. Examination revealed an ill-appearing, moderately obese young man. Temperature was 103.2 F orally. Blood pressure was "normal." There was a tachycardia of 110. White blood cell count was 30,350, with 79% polymorphonuclear leukocytes, 6% nonfilamented forms, 6% lymphocytes, 7% monocytes, 1% eosinophils, and 1% basophils. By 11 p. m., approximately six hours after the onset of symptoms, when examined at the hospital, the man was in no distress. Temperature was 99.8 F orally, and the pulse rate, 88 per minute. Blood pressure was 112/68 mm. of Hg. Except for a mild hyperemia in the pharynx, no other abnormalities were observed on this examination.

The following morning no abnormalities were found upon reexamination, and a repeated hemogram was normal. The urinalysis and roentgenogram of the chest were without abnormality. After a period of observation, during which time he continued to be asymptomatic, he was returned to duty.

Comment.—This patient, upon admission, was considered to have an acute infectious disease, and at first one might have been inclined to doubt that this represented an example of metal-fume fever despite the clarity and sequence of events in the history. Subsequently, however, it was learned at the shipyard that other men employed in the same task had experienced identical symptoms. Because the symptoms were less severe they had not sought medical attention, and since recovery was complete by the following day they paid no attention to them. Further confirmation was obtained by the findings in Case 3.

CASE 3.—A 22-year-old white man was referred to the U. S. Naval Hospital, Oakland, Calif., on June 21, 1956, with a diagnosis of "fever of undetermined origin." He had been employed in cleaning water tanks over a two-day period, using a steel wire buffing machine. A mask to prevent inhalation of dust had been worn. Forty-eight hours prior to his admission, on the first day of that duty, he experienced vague malaise, chilly sensations, and a feeling that his temperature was elevated. Following completion of duty that day he had a mild chill and a feeling of malaise which continued throughout the evening. The following morning, although the malaise persisted, he was sufficiently recovered to return to duty. During the second day the malaise worsened. He developed low back pain and a "dry, hacking," nonproductive cough. Upon arrival at home that evening he experienced a shaking chill and continued to have severe low back pain, aching of the muscles of the right shoulder, a dry cough, and severe malaise. A physician summoned to see the man referred him to a local dispensary with a diagnosis of "pneumonitis." At the dispensary he was found to have a temperature of 102.4 F orally, but the examination revealed no other pertinent abnormalities. At 1 a. m. he was transferred to the hospital. The physical examination then revealed an acutely ill young man. Temperature was 103.6 F orally. His face was flushed. The pulse rate was 104 per minute, and the blood pressure, 104/70 mm. of Hg in the right arm. No other significant abnormalities were disclosed. The white blood cell count was 21,400, with a differential of 59% polymorphonuclear leukocytes, 26% nonfilamented leukocytes, 13% lymphocytes, and 2% monocytes. Sedimentation rate was 6 mm. in one hour. A blood culture revealed no growth. Urinalysis and roentgenogram of the chest were within the limits of normal.

This patient was assigned to the contagious-disease ward and isolated. Four hours following admission he became afebrile and remained so throughout the first night and over the subsequent period of observation. By the following day he was completely asymptomatic. A repeated hemogram was normal.

Comment.—Initially this patient was thought to have pneumonia or an acute infectious process, and a blood sample for culture was drawn. It was not until the history and sequence of events were reevaluated and the course observed that the diagnosis was established. In Cases 2 and 3 the type of mask worn was inadequate. Both developed their illness at the end of the day or after reaching home. This is in accord with other reports, which indicate chills and fever uncommonly occur while a person is at work, but usually after he has reached home and sometimes after he has gone to bed.[2] Neither of these men, unlike the person in Case 1, had auscultatory abnormalities in the chest. Though they were acutely ill when first seen, both were sufficiently improved in 12 hours to have permitted their return to work. Their hospitalization was extended only for observation, and additional or residual symptoms or findings were not observed during the subsequent several days. It appears that the zinc dust created was of sufficiently small particulate size to produce the symptoms. One would doubt that the heat generated was sufficient to form zinc oxide in the usual manner.

Comment

Although it was known to the ancients that when zinc was burned white dust-like particles were formed, called "philosophers' wool," it was not until 1831 that "ague" following inhalation of freshly burned zinc fumes was first reported.[3] In 1845, one of the first accurate accounts of the symptoms, course, and benign nature of ague associated with the pouring of brass was reported. Considerable controversy existed, however, as to the exact cause of the malady until an experiment was performed by Lehmann, in 1906. Zinc was burned and vaporized under laboratory conditions, and zinc oxide was formed. Lehmann and four assistants, after exposing themselves to the fumes, experienced typical symptoms of ague, or what is now recognized as metal-fume fever. Similar experiments were performed by others.[3] A study by Drinker et al.[6-8] reported clinical observations on 10 persons subjected to known concentrations of freshly produced zinc oxide fumes. The symptoms which ensued were a sweetish taste in the mouth and a dry cough within 5 to 10 minutes after exposure. Six hours later substernal pain, nausea, and anorexia were observed, followed by headache, weakness, backache, chilliness, and fever reaching

a maximum of 102.8 F orally. The fever disappeared within 20 hours. Fine moist rales were heard beginning about one-half hour after inhalation. Three to five hours after exposure the white blood cell count reached 16,000. The leukocytosis gradually abated. Interestingly, the persistence of an elevated count was associated with a milder production of symptoms upon reexposure to zinc oxide fumes. Drinker's study also revealed a decrease in the pulmonary vital capacity during the acute phase of illness. In one case this was 53%, and in another, 18% below their norm. The pulmonary vital capacity returned to normal upon recovery from the acute stage. Zinc oxide as an etiologic factor was established, but the mechanism by which the symptoms were produced remained undetermined.

The dryness and irritation of the throat; substernal tightness; cough, wheezing, and rales, and decreased pulmonary vital capacity are undoubtedly due to physical irritative phenomena and bronchial constriction. The systemic features, less easily explained, are the subject of considerable speculation.

Lehmann postulated that the inhaled zinc oxide particles, because of their small size, reach the alveolar epithelial cells, where a destructive action occurs. The proteins thus formed when absorbed systemically presumably produce the symptoms. That bronchiolar and alveolar damage has occurred is suggested by the cases reported which have shown upper respiratory infections following an acute attack of metal-fume fever.

Particulate zinc entering the circulation via the lungs has been considered as a cause of the symptoms.[9] In support of this were the early experiments. Lehmann found zinc in the urine, and Arnstein recovered zinc from both urine and feces in subjects exposed to zinc oxide fumes. It is now known, however, that a normal person excretes zinc in the amount of 0.3 mg. per day in the urine and about 10 mg. per day in the feces. Refutation for this consideration exists, for intravenous administration of zinc causes no symptoms.[10]

The lack of similarity between inhaled and ingested zinc oxide has been reviewed extensively.[3] Nausea, vomiting, and substernal and abdominal pain with prostration follow ingestion. It may be that with exposure to zinc fumes some particulate matter is swallowed, and so a partial explanation exists for the nausea and vomiting sometimes seen in an acute attack.

Symptoms like those of metal-fume fever have not followed inhalation of ordinary zinc oxide powder. The large oxide particles apparently cannot readily pass through the bronchioles to reach the alveoli, a necessity for the production of symptoms. In freshly formed zinc oxide fumes the particles are dry and dispersed. Flocculation soon occurs, and large particles are formed. These also are incapable of causing the characteristic symptomatology.[3]

Symptoms resembling those occurring in metal-fume fever have been observed in a disease caused by a bacterium of the Aerobacter group or its products recovered from stained cotton dust.[11] This has suggested that bacteria or their products may be involved in the pathogenesis of symptoms in fume fever. That metals are capable of exhibiting a bactericidal effect on microorganisms, even in extreme dilution, is known. Naegeli, in 1893, is stated to have called this effect the oligodynamic action of heavy metals.[12] It has been postulated that the oligodynamic action of zinc exerts a toxic effect on the organisms of the lower respiratory passages and the absorption of the endotoxins liberated leads to the systemic features observed.[13] This speculation may be debated, for it has been found that in health the trachea, bronchi, and lungs are usually sterile.[14]

Of the aforenoted concepts of pathogenesis, Lehmann's protein-absorption theory appears to be the most reasonable.

The resemblance of metal-fume fever to an acute infection prompting the diagnosis of influenza, pneumonia, acute bronchitis, malaria, or a septic process is evident and warrants comment, as these must be considered in the differential diagnosis.[4]

The type of metal oxide and its concentration determine the severity of the attack.[5] With that produced by zinc oxide the recovery is complete within 24 hours, and lasting residual pulmonary damage in man has not been reported.[8,15] Certain sequelae, however, can be cited. Of the four cases reported by Kuh et al.,[13] one patient was hospitalized six days because of an ensuing upper respiratory infection. Pneumonitis followed an acute attack of metal-fume fever precipitated by welding on galvanized iron reported by Raine.[16] Subject "C" tested experimentally by Drinker et al.[7] had persistent pulmonary rales and roentgenographic findings of increased pulmonary vascular markings for several days following exposure to zinc oxide. Nevertheless, considering the extensive industrial use of zinc and the reports appearing in the literature, the incidence of ensuing respiratory sequelae must indeed be few. No authentic fatal case of metal-fume fever due to zinc oxide inhalation has been reported.[2] So-called "chronic poisoning" associated with zinc, mentioned in the earlier literature, is considered at present to be due to toxic impurities sometimes found in zinc ores, such as antimony, arsenic, cadmium, and lead.[15] These metals are capable of producing severe and even fatal metal-fume fever.[1]

Because of the benign nature and short duration of symptoms seen in metal-fume fever caused by zinc oxide, only symptomatic and supportive therapeutic measures have been advocated. It has been recommended that persons be treated "as though they had la grippe."[1] Relief may be afforded by using codeine, acetylsalicylic acid (aspirin), fluids, fruit juices, hot drinks, and bed rest. It is stated that an attack can at times be averted by a warm bath taken early in the course of the illness. Since chilling may initiate an attack, it was considered that a warm environment might prove beneficial. Drinker placed one of his subjects in a room having a humidity of 95% and a temperature of 100 F, following inhalation of zinc oxide fumes. No effect on the course of the ensuing illness was observed. An emetic and purge have been recommended.[9] Prevention and relief of symptoms, according to some, has followed ingestion of milk, sodium bicarbonate, and adequate fat in the diet.[3,9] The beneficial effect of many of these recommendations would be difficult to assess in view of the short duration and known spontaneous recovery.

Of greater importance is the prevention of this disease. Reducing fume concentration, limiting exposure time, maintaining adequate ventilation, and wearing proper protective respiratory devices are basic fundamental features.[2] The respiratory devices protecting against the pneumoconeoses, the Type A respirators approved by the Bureau of Mines, are considered inadequate. Type B mechanical-filter respirators are advised for fumes but without other precautions may be unsatisfactory. Drinker found that concentrations below 50 mg. of zinc per cubic meter rarely were associated with symptoms. Reduction of fume concentration to 15 mg. per cubic meter is recommended,[8] and an exposure time of eight hours to this concentration is considered safe.

Summary

Metal-fume fever due to zinc oxide is an acute, transitory, inhalant illness.

Irritation in the throat, substernal tightness, malaise, headache, muscle cramps, chills, and fever occur following exposure and usually disappear in 6 to 24 hours without ensuing complications or sequelae.

Three cases manifesting metal-fume fever due to zinc oxide are reported. One case was typical in that it followed exposure to the fumes produced in welding galvanized iron. Two cases are described which occurred following inhalation of dust formed when an abrasive steel-wire buffing machine was used in cleaning zinc-coated water tanks.

In the literature reviewed, confirmation of zinc oxide as an etiologic factor of this illness was found. Of the theories of patho-

genesis, that which attributes the symptoms to the absorption of proteins formed following the destructive action of zinc on the alveoli is most tenable.

Supportive treatment is recommended. Preventive measures consist of reducing fume concentration, limiting exposure, maintaining adequate ventilation, and using mechanical-filter respiratory devices.

U. S. Naval Hospital, Oakland, Calif.

REFERENCES

1. Hamilton, A., and Johnstone, R. T.: Industrial Toxicology, New York, Oxford University Press, 1946, pp. 614-616; 620; 663(21).

2. Sayers, R. R.: Metal Fume Fever and Its Prevention, Pub. Health Rep. 53:1080-1086 (July 1) 1938.

3. Drinker, P.: Certain Aspects of the Problem of Zinc Toxicity, J. Indust. Hyg. 4:177-197 (Aug.) 1922.

4. Gafafer, W. McK., Editor: Manual of Industrial Hygiene and Medical Service in War Industries, Philadelphia, W. B. Saunders Company, 1944, pp. 145-146.

5. Drinker, P.; Thomson, R. M., and Finn, J. L.: Metal Fume Fever: III. The Effects of Inhaling Magnesium Oxide Fume, J. Indust. Hyg. 9:187-192 (May) 1927.

6. Drinker, P.; Thomson, R. M., and Finn, J. L.: Metal Fume Fever: II. Resistance Acquired by Inhalation of Zinc Oxide on 2 Successive Days, J. Indust. Hyg. 9:98-105 (March) 1927.

7. Drinker, P.; Thomson, R. M., and Sturgis, C. C.: Metal Fume Fever: I. Clinical Observations on the Effect of the Experimental Inhalation of Zinc Oxide by 2 Apparently Normal Persons, J. Indust. Hyg. 9:88-97 (March) 1927.

8. Drinker, P.; Thomson, R. M., and Finn, J. L.: Metal Fume Fever: IV. Threshold Doses of Zinc Oxide, Preventative Measures, and the Chronic Effects of Repeated Exposures, J. Indust. Hyg. 9:331-345 (Aug.) 1927.

9. Osler, W.: Principles and Practice of Medicine: Designed for the Use of Practitioners and Students of Medicine, by H. A. Christian, Ed. 16, New York, Appleton-Century-Crofts, Inc., 1947, p. 545(45).

10. McCance, R. A., and Widdowson, E. M.: The Absorption and Excretion of Zinc, Biochem. J. 36:692-696 (Sept.) 1942.

11. Neal, P. A.; Schneiter, R., and Caminita, B. H.: Report on Acute Illness Among Rural Mattress Makers Using Low Grade, Stained Cotton, J. A. M. A. 119:1074-1082 (Aug. 1) 1942.

12. Salle, A. J.: Fundamental Principles of Bacteriology, Ed. 3, New York, McGraw-Hill Book Company, Inc., 1948, p. 175.

13. Kuh, J. R.; Collen, M. F., and Kuh, C.: Metal Fume Fever: Permanente Found. M. Bull. 4:145-151 (Nov.) 1946.

14. Stuart-Harris, C. H.; Pownall, M., Scothorne, C. M., and Franks, Z.: The Factor of Infection in Chronic Bronchitis, Quart. J. Med. 22:121-132 (April) 1953.

15. Batchelor, R. P.; Fehnel, J. W.; Thomson, R. M., and Drinker, K. R.: A Clinical and Laboratory Investigation of the Effect of Metallic Zinc, of Zinc Oxide, and of Zinc Sulphide upon the Health of Workmen, J. Indust. Hyg. 8:322-363 (Aug.) 1926.

16. Metal Fume Fever, Current Medical Literature, J. A. M. A. 137:1561 (Aug. 21) 1948.

Subarachnoid Hematoma Complicating Ruptured Intracranial Arterial Aneurysm

MURRAY B. BORNSTEIN, M.D., and MORRIS B. BENDER, M.D., New York

The syndrome of subarachnoid hemorrhage from ruptured intracranial aneurysm is well known. The symptoms vary; in some the symptoms are severe and progressive, in others the course may fluctuate. This fluctuation may be very conspicuous, so that after several days of relative improvement with lucidity there appears an increasing drowsiness or stupor. In these instances, one may conclude that there has been a recurrence of the intracranial bleeding, as confirmed by the reappearance or increase in the amount of blood in the cerebrospinal fluid. The downhill course, however, may be due to aneurysmal bleeding into the substance of the brain or into the subdural space. According to Logue [9] and Clarke and Walton,[3] hemorrhage from a ruptured aneurysm frequently extends into the subdural space. These extensions are small, form a very thin layer over the brain, and are usually found at autopsy. There are cases in which the subdural hemorrhages are much larger and are of themselves dangerous to the patient. In these cases of leaking aneurysm the recognition of a complicating subdural hemorrhage is extremely difficult. Clinically the question posed is whether the downhill course in a patient with a leaking aneurysm is due to (*a*) a persistent or recurrent bleeding into the subarachnoid space, (*b*) extension of bleeding into the brain substance, or (*c*) clot formation in the subdural space.

In order to answer these questions we reviewed the records of 20 cases of ruptured intracranial aneurysm which were available for pathological studies between 1927 and 1954 at The Mount Sinai Hospital. An analysis of these cases disclosed that in 10 instances of ruptured aneurysms the autopsy reported the dura as being normal. In one case there was no mention of the condition of the dura. Examination of the remaining nine cases indicated subdural blood as found in one at operation and in eight by postmortem study. Of these nine cases of ruptured aneurysm with subdural extension, four had small subdural hemorrhage and five had large or significant amounts of blood in the subdural space. The following are summaries of the nine cases of subdural clots in patients with subarachnoid hemorrhage due to a leaking aneurysm.

CASE 1.—The patient, a 31-year-old man, was admitted on Oct. 10, 1927, with a history of having been in coma for 48 hours. On admission the patient was comatose; both pupils were dilated and fixed to light. No corneal reflex could be obtained. A right facial paresis and rigidity of the right upper extremity were noted. A questionable right Babinski sign was present. Lumbar puncture showed a grossly bloody spinal fluid. The patient died soon after admission.

Postmortem examination revealed a ruptured aneurysm of the left anterior cerebral artery. The dura was under marked tension. When it was reflected, a considerable quantity of blood escaped. The subarachnoid space was filled with blood. There was a hemorrhagic cavity of the left frontal lobe, the hemorrhage having extended into the ventricular system.

Comments.—Because of the rapid onset of the hemorrhage and its massive character, we concluded that the clinical picture was caused by a ruptured aneurysm with erosion into the left cerebral hemisphere. Subdural hemorrhage was not considered.

CASE 2.—The patient, a 64-year-old woman, known to have been hypertensive for 12 years, was

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admitted on Dec. 17, 1927. Five days previously she had suddenly lost consciousness. This state lasted a few minutes and was followed by severe headache, persistent vomiting, and disorientation lasting 24 hours. Blood pressure on admission was 210/140. She was stuporous, irrational, and disoriented. In addition there were nuchal rigidity, bilateral papilledema, a right facial weakness, depressed deep tendon reflexes, absent right abdominal reflexes, and a questionable right Babinski sign. Lumbar puncture showed grossly bloody spinal fluid. Following admission there was a progressive downhill course for six days, terminating in coma and death.

Postmortem examination disclosed a ruptured aneurysm of the right middle cerebral artery about 2.5 cm. from its origin. The dura was markedly discolored and distended. When it was reflected, a considerable quantity of dark bloody fluid escaped. The subarachnoid space also contained a considerable quantity of blood. Examination of the brain revealed no other abnormality.

Comment.—In this case the illness lasted 11 days. Had the unsuspected subdural hematoma been recognized within the first few days after admission to the hospital, it is possible that evacuation might have saved the patient's life. This, of course, is problematic in view of the marked arterial hypertension.

CASE 3.—The patient, a 44-year-old woman, was admitted on Oct. 14, 1933. On Oct. 7, 1933, she had suddenly lost consciousness. Twenty minutes later she recovered, complained of severe headache and stiff neck, and vomited. On Oct. 13, 1933, she again became semistuporous. On admission there were noted nuchal rigidity, semistupor, a right palpebral fissure larger than the left, a left facial weakness, absent deep tendon reflexes, and a questionable left Babinski sign. The spinal fluid was pink and xanthochromic. Her hospital course was progressively downhill, and she died on Oct. 23, 1933, 16 days after the onset of her illness.

Postmortem examination revealed a ruptured aneurysm of the anterior communicating artery. The dura was under tension, and a thin subdural blood clot covered the convexity of the right hemisphere adjacent to the superior sagittal sinus from the precentral gyrus to the occipital pole. There was a thin film of subarachnoid hemorrhage over both hemispheres, with a small collection of fresh blood over the right gyrus rectus and under the right optic nerve and the optic chiasm. The gross substance of the brain was normal.

Comment.—In this case the illness lasted 16 days. It is possible that recognition and evacuation of this subdural hematoma might have changed the clinical course. The leak from the aneurysm was not massive.

CASE 4.—The patient, a 48-year-old man, was admitted on Feb. 24, 1942. Six hours before admission the patient suddenly lost consciousness for one to two minutes. On recovery he complained of severe headache and vomited. Three hours later he suddenly lapsed into deep coma. On admission the patient was comatose. Large vitreous and retinal hemorrhages were noted. There was generalized hyperreflexia with bilateral Babinski signs. Lumbar puncture revealed a grossly bloody cerebrospinal fluid under an initial pressure of over 40 mm. of water. The patient died on the day of admission.

Postmortem examination revealed a ruptured aneurysm at the bifurcation of the left internal carotid and anterior cerebral arteries. In the subdural space a large, nonadherent, jelly-like clot occupied the entire dorsolateral surface of the left hemisphere. In the subarachnoid space a large quantity of blood covered the entire brain. This collection was most marked over the anterior lobes and at the base. There was also a large hemorrhage into the left frontal lobe which had extended into the ventricular system.

Comment.—In this case the bleeding due to rupture of the aneurysm was very extensive. This alone might have been responsible for the death of this patient. The subdural hemorrhage was only a small extension of the intracranial bleeding. This patient would not have benefited by evacuation of subdural hematoma. Moreover, it is doubtful whether one would have the thought or time to find such a clot in a patient with a fulminating course of intracranial bleeding.

CASE 5.—A 51-year-old woman was admitted on Aug. 9, 1951. On Sept. 3, 1951, there had been an episode of sudden, severe, persistent headache accompanied by nausea and vomiting. A lumbar puncture at another hospital was reported as having revealed xanthochromic spinal fluid containing 8 RBC and 67 mg. per 100 cc. of protein. Only a right Babinski sign was noted. On admission to The Mount Sinai Hospital she was apathetic and dull. There was a right-sided weakness, including the face, and sensory deficits on the right. The deep tendon reflexes were hypoactive. Nuchal rigidity and a right Kernig sign were present. During her hospitalization, of 49 days, the patient's condition fluctuated considerably. There were also convulsive movements at various times. The spinal fluid was persistently bloody. On Sept. 4, 1951, a left percutaneous carotid angiogram was interpreted as showing a normal middle cerebral artery and an anterior cerebral artery

which was not distinctly abnormal. There was a questionable displacement of branches of the anterior cerebral artery, suggesting a frontal mass. On Sept. 19, 1951, the patient was semicomatose. She reacted to pinprick more on the left than on the right. There was a right Babinski sign. The pupils were dilated and fixed to light. The eyes were divergent. When the head was turned sharply to the right there occurred slight abduction of the left eye. Otherwise no eye movements could be obtained. On Sept. 22, 1951, the spinal fluid was again found to contain fresh blood. Her condition gradually deteriorated, and she died on Sept. 27, 1951.

Postmortem examination revealed two aneurysms. There was a ruptured aneurysm of the anterior communicating artery and an intact aneurysm of the left internal carotid artery. The subdural space contained firm, tenacious blood clotted over the inferior surface of the left hemisphere. There were slight, diffuse areas of subarachnoid hemorrhage over the convexity and at the base of the brain. The gyri over the convexity were slightly flattened, and the left uncus was herniated. Hemorrhage had occurred medial to the right frontal pole and into the left cingulate gyrus. Linear hemorrhages were also present in the midline of the tegmentum and into the pons.

Comment.—The subdural hematoma in this case was incidental. Its recognition and removal would not have benefited the patient.

Case 6.—The patient, a 52-year-old woman, was admitted on Jan. 1, 1952. On Dec. 27, 1951, she had suddenly lost consciousness. Several hours later she had some difficulty speaking, but was clinically well within 24 hours. A lumbar puncture at that time yielded grossly bloody spinal fluid. On Dec. 31, 1951, the right side of her body suddenly became weak, and speech difficulties returned. She gradually lapsed into stupor.

On admission the patient was stuporous. The blood pressure was 140/100. There was nuchal rigidity accompanied by Brudzinski and Kernig signs. There were also a right facial flattening, a right hemiparesis, and a questionable right Babinski sign. On Jan. 3, 1952, a left frontal-parietal exploration for a possible intracerebral hematoma was performed. At operation, the dura was noted to be discolored a greenish-black. It was incised, and a relatively thin layer of jelly-like subdural clot was removed. There was no surface indication of underlying or intracerebral clot, nor was any found on subsequent exploration by needle or transcortical incision. Following surgery the patient continued in deep stupor and died on Jan. 5, 1952.

Postmortem examination disclosed a ruptured aneurysm of the left middle cerebral artery 18 mm. from its point of bifurcation with the anterior cerebral artery. There was hemorrhage on both sides of the dura. Subarachnoid hemorrhage was described at the base of the brain, in the left Sylvian fissure, and at the operative site. The gyri were flattened, and the brain had herniated through the operative defect. An acute encephalomalacia of the left parietal lobe with anatomical disruption of tissues related to the operative procedures were noted. No intracerebral extension of the bleeding was noted.

Comment.—The clinical diagnosis in this case was cerebral hemorrhage, but the finding of an unsuspected subdural hematoma seemed to be a satisfactory explanation for the clinical syndrome. However, the removal of the subdural clot was ineffective. The unsuspected ruptured aneurysm with bleeding into the subarachnoid space was the cause of death.

Case 7.—The patient, a 47-year-old woman, was admitted on March 22, 1952, because of persistent headache of three weeks' duration. On Jan. 26, 1952, the patient complained of sudden severe headache "all over the head." The symptom persisted until Feb. 14, 1952. On Feb. 18, 1952, the severe headache suddenly recurred, associated with blurring of vision to the left and a feeling of "thickness" over the left side of the face. The last two symptoms subsided, but the headache and slight photophobia persisted.

On admission the blood pressure was 128/80. Neurological examination revealed a stiff neck with Brudzinski and Kernig signs, a left homonymous hemiamblyopia by confrontation, normal fundi, a left Babinski sign, and obscuration of pinprick appreciation in the left upper extremity on double simultaneous stimulation. A lumbar puncture yielded grossly bloody spinal fluid containing 47 mg. per 100 cc. of protein in the slightly yellow supernatant fluid.

The clinical picture remained unchanged for three days. On March 25, 1952, she complained of severe headache and suddenly became deeply comatose. There were recurring extensor movements of all four extremities. The eyes were divergent. The left pupil was dilated, while the right was miotic; neither reacted to light. There was a left Babinski sign. The neck was not stiff. An electroencephalogram was reported as normal. A lumbar puncture yielded slightly cloudy spinal fluid under an initial pressure of 600 mm. of water. The supernatant fluid was yellow. A cisternal puncture yielded grossly bloody fluid. Later that day questionable hemorrhages were observed in the optic fundi. The eyes did not move relative to the head. The patient died early in the morning of March 26, 1952.

Postmortem examination showed an easily removed subdural clot. Slight areas of subarachnoid hemorrhage were diffusely present over both convexities, but a considerable amount of clotted blood was found at the base. In the parenchyma of the brain there was a large hemorrhage into the left temporal lobe; small hemorrhages into the tegmentum of the pons, probably into the midbrain, and into the base of the pons, and a series of small hemorrhages into the tegmentum of the medulla. There were two aneurysms. There was a ruptured aneurysm at the bifurcation of the left internal carotid artery and an intact aneurysm similarly located on the right.

Comment.—The subdural hematoma was small and probably not significant in this case.

CASE 8.—The patient, a 50-year-old woman, was admitted on March 22, 1952, in coma. The patient had been apparently well until March 1, 1952, when she was hospitalized elsewhere for three days with the complaints of nausea, vomiting, and fever. After discharge she continued to be nauseated, vomited occasionally, and persistently complained of headache. On the day of admission she had experienced a single episode of pain in the eyes, dizziness, and a "fainting spell." Later she was found in coma with a laceration of the scalp over the left parietal region. One-half hour after admission the coma was observed to be lessening. The deep tendon reflexes, which had been absent, returned, and the previously pinpoint pupils were slightly dilated. There was frequent vomiting. Two hours after admission she was conversing, complained of headache, and was markedly confused. The blood pressure was 130/88. Examination revealed a lethargic, disoriented patient with a moderately stiff neck and Kernig's sign. The fundi were normal, as were the eye movements. There was a slight facial asymmetry. Tendon reflexes were active in the upper and depressed in the lower extremities. Bilateral Babinski signs were elicited. Sensation was intact. A lumbar puncture revealed grossly bloody spinal fluid under a pressure of 600 mm. of water. The supernatant xanthochromic fluid contained 460 mg. per 100 cc. of protein.

During the next 48 hours the patient became alert and complained of stiff neck and mild headache but was otherwise unchanged. An electroencephalogram was reported as normal on March 24, 1952. On March 26, 1952, she again had a severe headache and vomited. A lumbar puncture again revealed grossly bloody fluid under 60 mm. of water pressure, xanthochromia, and a protein content of 450 mg. per 100 cc. On March 29, 1952, the patient complained of sudden severe headache and passed into coma within two minutes. The eyes were divergent and did not move when the head was passively turned. The pupils were in mid-dilatation and did not react to light. No corneal reflex could be obtained. Spinal fluid was still grossly bloody and under a pressure of 130 mm. of water. The patient remained in deep coma and died the following day.

Postmortem examination demonstrated a ruptured aneurysm of the anterior communicating artery. A portion of the dura was present and noted to have easily removed clotted blood on both aspects. A marked subarachnoid hemorrhage covered the entire convexity and filled the basal cisterns. Intracerebral extension of the hemorrhage had occurred into the frontal lobe through a tear in the parasagittal area.

Comment.—Again, the subdural hematoma was of little clinical significance. It was the hemorrhage into the subarachnoid space and the frontal lobe which caused death.

CASE 9.—The patient, a 59-year-old man, was admitted to The Mount Sinai Hospital for the second time on Feb. 12, 1954. In December, 1948, he experienced a sharp severe occipital pain during an attack of coughing. One week later, a similar incident occurred, this time followed by low back pain which radiated into the right thigh. Within another week the patient complained of a mild vertex headache. Shortly thereafter he was found unconscious in the bathroom. He regained consciousness after about an hour, at which time it was noted that he had difficulty moving the right arm and could not speak properly. He was then admitted to The Mount Sinai Hospital. The blood pressure was 140/86. The neurological examination revealed aphasia, apraxia, a stiff neck with bilateral Kernig signs, poor finger movements on the right, hypalgesia on the right side of the face, a right homonymous hemianopia to confrontation, and a slight increase in the deep tendon reflexes on the right. No pathological reflexes were noted. A lumbar puncture yielded grossly bloody spinal fluid under a pressure of 290 mm. of water. An attempted carotid angiogram was unsuccessful. An electroencephalogram on Dec. 17, 1948, revealed a focal lesion of the left frontotemporal region. He improved during his hospital stay. A repeat electroencephalogram on Jan. 5, 1949, was reported as normal.

When seen in the follow-up clinic on July 14, 1949, the patient complained of periodic left occipital headaches but was otherwise asymptomatic and revealed no abnormal findings. He remained otherwise well until the date of his second admission.

On Feb. 12, 1954, the patient was found comatose in his car. He was brought to the hospital, where he was noted to be stuporous, reacting only to painful stimuli. The blood pressure was 140/90.

There were also noted a right hemiplegia and hemisensory syndrome, generalized deep tendon hyperreflexia and a right Babinski sign. The pupils were small and reacted sluggishly to light. The fundi were normal. No nuchal rigidity was present. The day following admission the patient was in deep coma. A left stellate ganglion block on Feb. 14, 1954, produced only "a mild dilatation of the left pupil lasting two hours." On Feb. 15, 1954, the patient became hyperthermic and died.

Postmortem examination revealed a large ruptured aneurysm of the left middle cerebral artery in the region of the basal ganglia. On the inner surface of the dura there was a dry, focal chocolate-colored area apparently due to old blood. An extensive subarachnoid hemorrhage covered both hemispheres, but was greater on the left. Adjacent to the aneurysm, hemorrhage had penetrated the left frontal and temporal lobe.

Comment.—The subdural hematoma in this case was of minor significance. The major bleeding was into the subarachnoid space and left cerebrum.

In the foregoing nine cases, there were two patients who had 2 aneurysms, there being a total of 11 aneurysms described in the postmortem examinations. They were distributed as follows: internal carotid, four; anterior cerebral, one; middle cerebral, three; anterior communicating, three. Neither in these 9 cases of aneurysm with subdural hematoma nor in the 11 cases without subdural hematoma was there any apparent relationship between the location of the aneurysm and the clinical course. The symptoms varied according to location and severity of hemorrhage. In analyzing the clinical data of the cases with and without subdural hematomas, there seemed to be no characteristic difference between the two groups in regard to onset, signs, symptoms, and the clinical course. These patients were all classified as having intracranial bleeding from a ruptured aneurysm. Subdural hematoma was not considered in the differential diagnosis. One should consider the possibility of subdural hemorrhage as a complication of ruptured aneurysm, since, in some instances, the removal of the clot may be life-saving. The following two cases are examples.

CASE 10.—The patient, a 53-year-old woman, was admitted on July 9, 1954, in coma. Although the patient had always had headaches characterized as "migraine," no other neurological complaints had been experienced until the day of admission, when she was found unconscious.

On admission to the hospital the patient was semistuporous, disoriented, and complaining of severe headache. There were fresh retinal hemorrhages, a mild left hemiparesis, and a left Babinski sign. Lumbar puncture showed gross blood in the cerebrospinal fluid.

During the next eight days the patient improved. She became alert and oriented. The hemiparesis lessened, but the left Babinski sign persisted. An x-ray of the skull on July 16, 1954, revealed a calcified pineal body shifted from right to left. On July 17, 1954, there rapidly developed a complete left-sided sensorimotor syndrome with a left homonymous hemianopia, nuchal rigidity, drowsiness, and disorientation. This was thought to be due to a recurrence of the subarachnoid hemorrhage. However, a lumbar puncture showed the spinal fluid to be clear, pale yellow, and under a pressure of 280 mm. of water; it contained no RBC, 11 WBC, and a protein of 31 mg. per 100 cc.

There was little improvement during the following nine days. On July 29, 1954, there occurred a right-sided convulsion, following which the patient became comatose. At that time the spinal fluid was grossly bloody. A right percutaneous carotid angiogram demonstrated a small aneurysm of the internal carotid artery just proximal to the origin of the posterior communicating artery. This examination was followed by double ligation and section of the right common carotid artery. Two days later the patient was responsive and complained of headache. There was nuchal rigidity and a total left hemiplegia. The fundi were normal. The cerebrospinal fluid was still grossly bloody, but less so than on July 29, 1954. During the following 48 hours the mental state fluctuated considerably from periods of semistupor and verbal responsiveness to coma and Cheyne-Stokes respiration. On Aug. 1, 1954, the cerebrospinal fluid was found to be xanthochromic, under increased pressure, but without evidence of fresh bleeding. Because of this fluctuating state and decreased bleeding in the subarachnoid space an intracerebral hematoma was suspected. However, on subtemporal craniectomy a partially organized and partly fluid hematoma 1 cm. in thickness was evacuated. A ventricular needle puncture of the anterior, inferior portion of the right temporal lobe disclosed a hard area palpated at about 5 cm. depth. It was decided not to attempt its removal.

Following operation the patient continued to improve steadily, so that on Aug. 3, 1954, she was talking and oriented. On Aug. 5, 1954, the patient again became drowsy, disoriented, and increasingly

febrile. The cerebrospinal fluid was again grossly bloody. Since x-ray showed no alteration in the position of metal clips strategically placed during operation, no further procedure was done. On Aug. 8, 1954, x-ray showed the pineal returned to the midline.

During the following four weeks of hospitalization there was slow steady improvement. No further episodes of alteration in consciousness occurred. The patient was discharged on Sept. 8, 1954. She spoke rarely, but her speech was appropriate, and there was a general appearance of alertness. There remained a complete left hemiplegia and a left homonymous hemianopia. The fundi were normal, and the decompression was soft and pulsating. Since discharge there has been slight improvement in the neurological status. In January, 1956, the patient had a residual left hemiplegia.

Comment.—Although carotid angiography demonstrated the arterial aneurysm, careful *post hoc* studies of the angiogram revealed no evidence of a subdural hematoma. It is possible that the subdural hemorrhage may have occurred after the arteriogram, since there was clinical and spinal fluid evidence of bleeding following carotid ligation and section. At operation the subdural hematoma was an unexpected finding. The exploration was performed for a suspected intracerebral hematoma, but the patient's condition did not permit exploration after the subdural clot had been removed. However, since the shifted pineal returned to its normal position and the patient's clinical state improved, it seemed logical that the deviation of the pineal body was due to the subdural hematoma. In this case it was impossible to differentiate between the syndrome of leaking aneurysm, cerebral hemorrhage, and complicating subdural hematoma even with the aid of an arteriogram.

CASE 11.—The patient, a 38-year-old woman, was admitted on Feb. 27, 1955, with the chief complaint of left-sided weakness and severe headache of 24 hours' duration.

The patient had enjoyed good health until Feb. 13, 1955, when she complained of generalized weakness, apathy, and "heartburn." The symptoms continued for seven days. On Feb. 21, 1955, there suddenly developed a severe headache associated with nausea, vomiting, and drowsiness. Her husband noted two momentary episodes of staring, stiffness of the body, mumbling, and drooping of the left side of the face. During the next two to three days the symptoms disappeared. On Feb. 27, 1955, the patient again complained of sudden severe headache and drowsiness. The left side of the face drooped. Soon the symptoms progressed to stupor. A paralysis of the left upper and a weakness of the left lower extremity ensued. She was then referred to The Mount Sinai Hospital for study and treatment. Examination on admission showed the patient's general appearance to be that of a well-developed, well-nourished, middle-aged woman. There was no abnormality outside the nervous system. The blood pressure was 110/70. The temperature was 99 F.

The patient was somnolent but cooperative and oriented. When asked to identify touch stimuli simultaneously applied to the cheek and the dorsum of the opposite hand, the patient frequently made errors even with her eyes open. Thus, she either did not perceive the hand stimulus (extinction) or referred it to the homolateral cheek (displacement). There were slight signs of meningeal irritation. A left homonymous visual field defect to red stimuli was thought to be present on simple confrontation tests. The appearance of the fundi and the pupillary reactions were normal. Although the eyes exhibited a full range of movement, they were usually held in right conjugate gaze. No nystagmus was present. There was a left hemiparesis which included the face. There was a left hyperreflexia and concomitant Babinski and Hoffmann signs. Sensation was intact to all modalities.

During the day of admission, Feb. 27, 1955, the patient became alert. The slight signs of meningeal irritation disappeared. No visual-field defect could later be demonstrated, although the left-sided weakness and hyperreflexia persisted. Lumbar puncture yielded xanthochromic cerebrospinal fluid under an initial pressure of 230-270 mm. of water, containing 620 RBC and 3 lymphocytes per cubic millimeter, and a protein of 45 mg. per 100 cc.

The day after admission, Feb. 28, 1955, a right percutaneous carotid angiogram demonstrated a large aneurysm situated near the origin of the right anterior, middle, and posterior cerebral arteries. In the anteroposterior projection the anterior cerebral artery was seen to be slightly deviated to the left. The middle cerebral artery was not raised, nor was there x-ray evidence characteristic of a subdural hematoma.

The improvement in signs and symptoms continued until March 1, 1955, when the patient suddenly became totally paralyzed on the left side of the body without any alteration in the state of consciousness. Later that day a left percutaneous carotid angiogram revealed a second aneurysm at the bifurcation of the left internal carotid and middle cerebral arteries. Only a lateral study was

done. Shortly thereafter the right common carotid artery was doubly ligated and sectioned under local anesthesia.

The following day the patient responded to questions but was somewhat drowsy and disoriented. She strongly denied the persistent hemiplegia. She complained of headache and stiff neck. During the subsequent 48 hours there was a gradually progressive deterioration. There appeared a left homonymous hemianopia and a right oculomotor paralysis. The left side of the body became increasingly spastic, and, finally, there developed hyperactive segmental reflexes and decerebrate movements. She lapsed into stupor and then coma. A lumbar puncture on March 4, 1955, revealed crystal clear but slightly yellow cerebrospinal fluid under an initial pressure of 90 mm. of water. The fluid contained 9 RBC, 17 lymphocytes, 8 P. M. N. per cubic millimeter, and a protein of 25 mg. per 100 cc.

In view of our experience with Case 10, which was observed several months previously, and because of the patient's critical condition and the lack of evidence of fresh subarachnoid hemorrhage, the possibility of a subdural hematoma was considered. Therefore, on March 5, 1955, a temporal craniectomy was performed, and a very large, liquid and clotted subdural hematoma was found and evacuated. The left side of the head was then trephined, but no abnormal collection of blood was found. No further operative procedure was thought advisable at this time.

For two weeks after the operation the patient weathered a stormy course with coma, hyperthermia, total left hemiplegia, partial right hemiparesis, and a complete right oculomotor nerve palsy. The usual antibiotic and supportive measures were carried out. Since about March 19, 1955, there has occurred a slow but steady improvement, with minor fluctuations. Within three months the oculomotor palsy disappeared. One year later there remains a total left hemiplegia and a partial weakness of the right arm and leg. Numerous bedsores have responded to therapy. Mentally she is alert, and she converses easily with her husband on such subjects as music and art. With physical therapy and body care, the patient continues to be unchanged.

Comment.—In Cases 10 and 11, carotid angiography demonstrated arterial aneurysms but did not suggest the presence of a subdural hematoma. Since there occurred a change in symptoms following carotid ligation in both of these patients, it is possible that the change was caused by subdural bleeding. Preoperatively it was impossible to distinguish subarachnoid hemorrhage, intracerebral hematoma, and subdural bleeding, even with the aid of arteriography. The postoperative recovery following removal of the subdural hematomas in Cases 10 and 11 was neither as rapid nor as complete as is usually seen in uncomplicated cases. Although the improvement in mental function has been marked in both patients, it is probable that the hemiplegias will be permanent. The permanence of the neurological deficits, hemiplegia in these two cases, may have also been caused by ligation of the carotid artery. Nevertheless, it would seem that the evacuation of the subdural hematomas was life-saving.

Comment

Although Munro's[10] extensive study of subdural hematoma did not mention ruptured intracranial arterial aneurysm as a possible cause, individual cases had already been reported.[6,12-14] Later, other series were published.[2,4,8] With the impetus of possible preoperative diagnosis afforded by carotid angiography and the successful treatment of the condition in a number of cases, statistical studies and series have begun to appear.[1,3,5,11] The frequency of occurrence of this condition has been reported in two ways. First, its incidence in those cases of intracranial hemorrhage due to ruptured aneurysms has been calculated. Bassett and Lemmen[1] reported 5 subdural hematomas in 63 cases of surgically treated aneurysms (about 8%); Clarke and Walton,[3] 6 cases in 312 of subarachnoid hemorrhage due to aneurysm (about 2%); while Golden et al.[5] found 7 cases of subdural bleeding in 334 cases of intracranial aneurysms (about 2%). Wilson, Riggs, and Rupp[15] list 22 instances of subdural hemorrhage in 143 autopsied cases of subarachnoid bleeding due to ruptured intracranial arterial aneurysms (about 15%). Hazouri[7] reviewed 72 patients with ruptured intracranial aneurysms. Among these, five cases of massive subdural hematoma were encountered. In our series of 20 autopsied cases, subdural extension occurred in 9

instances. Of these, only two were probably of clinical significance.

Another method of classification is to determine the incidence of aneurysm as a cause of subdural hematoma. Logue [9] considers intracranial aneurysm as second only to trauma in etiologic importance. He states that about 8% of all subdural hematomas are produced by ruptured intracranial aneurysms. There may, on occasion, be minimal or no accompanying subarachnoid hemorrhage. Case 11 of our series showed minimal subarachnoid bleeding; the major portion of intracranial bleeding appeared to be in the subdural space. Poppen [11] reported 3 cases of subdural hematoma produced by ruptured intracranial aneurysm in a total of 119 patients treated surgically for subdural hematomas. Evidently subdural hemorrhage in cases of intracranial aneurysms is not too uncommon. However, there are many types, some of which are not clinically significant. Clarke and Walton [3] divided these into three groups: (*a*) small clinically insignificant amount of subdural blood, (*b*) a massive and rapidly fatal subdural hemorrhage, and (*c*) clinically significant subdural hematoma which is not rapidly fatal. It is the last type which requires special attention. As was pointed out, clinically it was impossible to distinguish cases of subarachnoid bleeding with or without subdural hemorrhage. Moreover, arteriography in Cases 5, 10, and 11 did not disclose the typical angiographic signs of a subdural hematoma. The absence of angiographic evidence for subdural hematoma in Cases 10 and 11 is especially disturbing. It must be admitted, however, that the subdural bleeding may have occurred after carotid angiography was performed. In essence, a study of the clinical aspects of these cases as well as those autopsied cases of ruptured aneurysms without subdural hematomas agrees with the generally reported conclusion that there are few, if any, specific features of a subdural hematoma associated with subarachnoid and possibly intracerebral hemorrhage. Except in Case 11, the presence of a subdural hematoma was a surprise finding in all instances.

In conclusion one must realize (*a*) that subdural hemorrhage is a possible complication of a leaking intracranial aneurysm and (*b*) that this complication is difficult to recognize even with the aid of arteriography.

Summary

Clinically significant subdural hematomas may be associated with intracranial bleeding due to ruptured arterial aneurysm.

Between the years 1927 and 1954 at The Mount Sinai Hospital, New York, postmortem examinations were conducted on 20 patients diagnosed as having ruptured intracranial arterial aneurysms. Of these, nine showed extension of bleeding into the subdural space. Of the nine, there were five cases of clinical significance. There were also two cases in which the removal of subdural hematoma as a complication of leaking aneurysm possibly saved the patient's life.

No significant clinical features characterize those patients in whom subdural extension has occurred, yet its presence should be suspected and investigated in those whose clinical course is unsatisfactory.

REFERENCES

1. Bassett, R. C., and Lemmen, L. J.: Subdural Hematoma Associated with Bleeding Intracranial Aneurysm, J. Neurosurg. 9:443-450, 1952.

2. Case Records of the Massachusetts General Hospital, Case 28151, New England J. Med. 226: 613-616, 1942.

3. Clarke, E., and Walton, J. N.: Subdural Hæmatoma Complicating Intracranial Aneurysm and Angioma, Brain 76:378-404, 1953.

4. Courville, C. B., and Olsen, C. W.: Miliary Aneurysm of the Anterior Communicating Artery: A Clinical-Pathological Report of 19 Cases, 18 with Fatal Hemorrhage, Bull. Los Angeles Neurol. Soc. 3:1-27, 1938.

5. Golden, J.; Odom, G. L., and Woodhall, B.: Subdural Hematoma Following Subarachnoid Hemorrhage, A. M. A. Arch. Neurol. & Psychiat. 69:486-489, 1953.

6. Hassin, G. B.: The Pathogenesis of Cerebral Hemorrhage: A Case of Aneurysm of the

Posterior Communicating Artery, Arch. Neurol. & Psychiat. 17:770-782, 1927.

7. Hazouri, L. A.: Review of 75 Intracranial Aneurysms, J. M. A. Georgia 44:15-19, 1955.

8. Irish, C. W.: Aneurysms of the Cerebral Vessels with a Study of 32 Cases Found at 12,503 Consecutive Necropsies, Ann Arbor, Mich., Edwards Brothers, Inc., 1940.

9. Logue, V.: Chronic Subdural Effusions, in Modern Trends in Neurology, edited by A. Feiling, London, Butterworth & Co., Ltd., 1951, pp. 363-390.

10. Munro, D.: The Diagnosis and Treatment of Subdural Hematomas, New England J. Med. 210:1145-1160, 1934.

11. Poppen, J. L.: Chronic Subdural Hematomas, Geriatrics 10:49-51, 1955.

12. Sosman, M. C., and Vogt, E. C.: Aneurysms of the Internal Carotid Artery and the Circle of Willis from a Roentgenological View-Point, Am. J. Roentgenol. 15:122-134, 1926.

13. Strauss, I.; Globus, J. H., and Ginsburg, S. W.: Spontaneous Subarachnoid Hemorrhage: Its Relation to Aneurysms of the Cerebral Blood Vessels, Arch. Neurol. & Psychiat. 27:1080-1132, 1932.

14. Symonds, C. P.: Contributions to the Clinical Study of Intracranial Aneurysms, Guy's Hosp. Rep. 73:139-158, 1923.

15. Wilson, G.; Riggs, H. E., and Rupp, C.: The Pathologic Anatomy of Ruptured Cerebral Aneurysms, J. Neurosurg. 11:128-134, 1954.

16. Wright, C. J. E.: Coarctation of the Aorta with Death from Rupture of a Cerebral Aneurysm, Arch. Path. 48:382-386, 1949.

Metallic Mercury Embolization—Clinical and Experimental

CAPT. MARCEL E. CONRAD Jr. (MC), U. S. Army; CAPT. JAY P. SANFORD (MC), U. S. Army (Res.), and CAPT. JOSEPH A. PRESTON (MC), U. S. Army (Res.)

General medical interest in mercury poisoning is primarily limited to the toxicity of the various salts of mercury. Metallic mercury is often considered to be quite inert if deposited in tissues. Toxicity, however, is apparent by most routes of administration, including inhalation, ingestion, and injection.

The inhalation of vaporized metallic mercury is the most commonly discussed form of toxicity. Chronic inhalation is primarily an industrial and laboratory hazard. The onset of symptoms is often insidious. Common symptoms include behavioral changes, insomnia, mental depression, and occasionally hallucinations. These symptoms may be associated with anemia, renal tubular damage, stomatitis, colitis, and peripheral neuritis.[6,7]

Acute inhalation of vaporized mercury may be rapidly lethal. Campbell reported acute pulmonary edema in an infant whose parents dropped mercury on a hot stove to watch it vaporize. In addition to pulmonary edema, degeneration of the renal convoluted tubules and necrotic changes in the gastric and duodenal mucosa were noted at postmortem examination.[2]

The absence of symptoms produced by metallic mercury in the gastrointestinal tract has been stressed.[7] From the mid-17th century until the mid-19th century, metallic mercury was used in the treatment of intestinal obstruction.[5,15] Recently, Birnbaum reported a patient with appendicitis secondary to metallic mercury.[1] Lindemuth studied a patient with persistent fecal fistula following leakage of metallic mercury from an intestinal tube.[11]

Subcutaneous deposition of mercury causes chronically draining lesions. Broken thermometers are the most common cause. Small abscesses containing leukocytes, macrophages, occasional epithelioid cells, and occasional foreign-body giant cells have been described. Mercury particles may or may not be demonstrable. These lesions are occasionally associated with mild systemic findings referable to the central nervous system, gastrointestinal tract, or kidneys.[9]

Lathem reported two instances in which accidental arterial embolization occurred while blood samples were being obtained with syringes containing mercury.[10] The extremities became reddened, swollen, and tender. Sterile subcutaneous abscesses developed from which small particles of mercury were extruded. No symptoms suggestive of systemic involvement were noted.

Intravenous embolization with metallic mercury, while very uncommon, seems to produce more acute symptoms. Sitson reported a patient who died six days after the intravenous injection of 150 mg. of mercury in 40% oil of cinereum. Metallic mercury was found in the lung at the time of autopsy.[12] Umber and Konig studied a girl who attempted suicide by the intravenous injection of 2 ml. of mercury.[9,14]

The observation of intravenous mercury embolization in a patient led to studies on

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Division of Medicine and Division of Surgery, Walter Reed Army Institute of Research, and Department of Medicine, Walter Reed Army Hospital, Walter Reed Army Medical Center, Washington 12, D. C.

its pathogenesis in dogs. The striking clinical features of the patient and the interesting experimental findings form the basis of this report.

Report of Case

A 26-year-old radar mechanic was admitted to a service hospital in the Far East on April 29, 1955, with primary complaints of shortness of breath, weakness, and fever for one day. The previous morning he awoke with a severe headache and generalized weakness. Upon arising, he vomited a small amount of yellowish fluid. This he attributed to the intake of excessive alcohol on the previous night. During the day he developed fever, chills, and anorexia.

He had a chronic cough following recovery from pertussis at age 6. There was a history of questionable hemoptysis a year before admission. During the preceding two months, he was seen in a dispensary several times because of a persistent cough and chest pain. He was also being seen as an outpatient in the Neuropsychiatric Clinic because of difficulties diagnosed as a schizoid personality. In addition, he gave a history of excessive alcohol ingestion and recurrent gastritis.

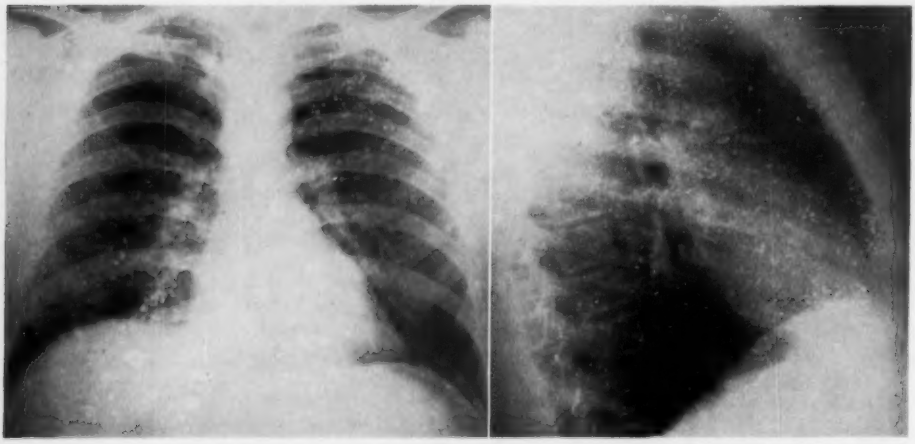
On admission the patient was a well-developed, well-nourished, white man with a dry, hacking cough. The blood-pressure was 108/70; pulse, 100 per minute; temperature, 102.8 F. The respirations were short and shallow, at 36 per minute. Fine, crepitant rales were noted over the right lower anterior chest. Marked bilateral costovertebral angle tenderness was present. The remainder of the physical examination was within normal limits.

The patient's white cell count on admission was 21,650 per cubic millimeter, with 92% polymorphonuclear leukocytes; hemoglobin, 14.1 gm/100 cc.; hematocrit, 45%, and sedimentation rate, 37 mm. per hour. Urine showed 1+ albumin and 10 to 12 WBC per high-power field. Bacteriologic cultures of blood and urine were negative.

A chest x-ray revealed diffuse metallic globules throughout both lung fields. The patient attributed this to aspiration of metallic mercury in approximately August, 1954, when he was startled while sucking mercury into a straw. However, a chest x-ray was reported as normal in November, 1954, and an upper gastrointestinal series was normal in February, 1955.

He was given intramuscular penicillin for seven days. By May 2 he became afebrile but continued to complain of cough, shortness of breath, and pleuritic-like pain. His vital capacity was 1140 cc. and maximum breathing capacity, 47 liters per minute. Urinalysis became negative by May 4. At this time liver-function studies showed 15% retention of sulfobromophthalein in 45 minutes, serum albumin of 2.82 gm/100 cc., serum globulin of 3.73 gm/100 cc., and normal flocculation tests. The patient became asymptomatic by May 6. White blood cell count at this time was 8250 per cubic millimeter, with a normal differential. Vital capacity was 2075 cc., with a maximum breathing capacity of 51 liters per minute. Stools were positive for traces of mercury on May 31. A 3×3 cm. grayish mass was noted in the left antecubital fossa on June 3. Biopsy was done on this, and the specimen contained approximately 0.2 ml. of metallic mercury. X-rays showed globular metallic densities in this area. Pulmonary function improved slowly, until on June 21 his

Fig. 1.—Posteroanterior and lateral roentgenograms of patient at time of admission to Walter Reed Army Hospital (July, 1955).



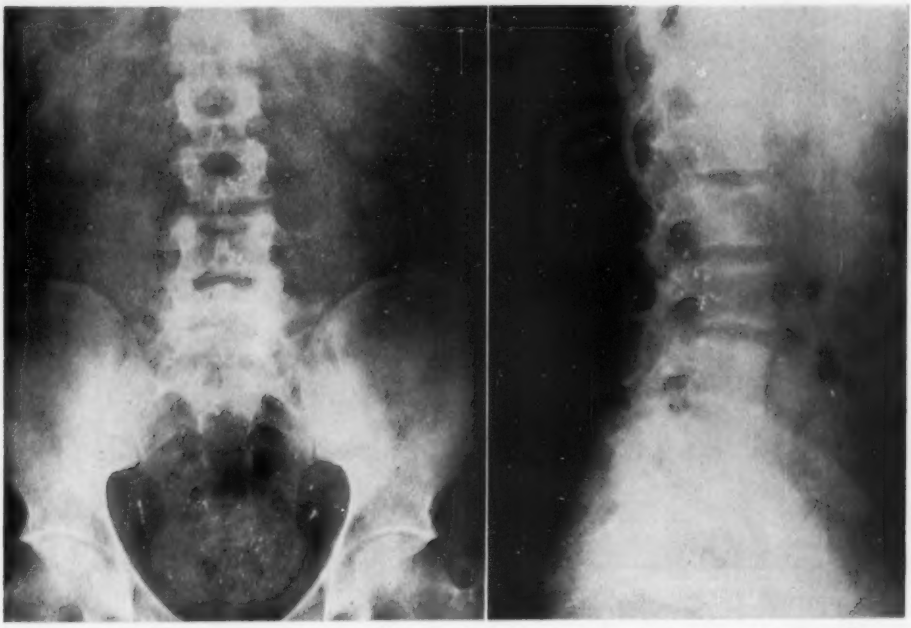


Fig. 2.—Roentgenograms of the abdomen, demonstrating metallic particles in the pelvic and paravertebral vessels.

vital capacity was 3800 cc., with a maximum breathing capacity of 109 liters per minute. Hemogram, urinalysis, and repeated liver-function studies have remained normal. The patient denied self-administration of metallic mercury by the intravenous route on many occasions, including during an amobarbital (Amytal) interview. In mid-July he was transferred to the Neuropsychiatric Service of Walter Reed Army hospital. He was asymptomatic. His physical examination was also normal. Hemogram and liver-function tests were normal. The serum albumin was 5.0 gm/100 cc.; serum globulin, 2.8 gm/100 cc. A 24-hour stool specimen contained 0.05 mg. of mercury. X-rays of the chest still showed extensive deposite of small, globular, metallic fragments in both lung fields (Fig. 1). Films of the abdomen revealed similar densities, which were felt to follow the course of the vertebral and pelvic veins (Fig. 2). There were similar subcutaneous deposits in the left antecubital fossa. Films of the skull, hands, and feet were normal.

In August, urinary PSP excretion, concentrating ability, daily urinary albumin, and an endogenous creatinine clearance were normal. Repeated urine specimens contained occasional hyaline casts. Addis counts showed 8000 to 10,000 casts on 12-hour specimens.

Experimental Studies

Clinical, roentgenographic, pathologic, and toxicologic studies were carried out in dogs to study the effects of metallic mercury embolism. Mercury (2 ml.) was administered intravenously to six dogs, endotracheally to one, and subcutaneously to one. These dogs either died before or were killed after 28 days of observation. Another dog received only 0.5 ml. of mercury intravenously. This animal was kept six months to study the chronic effects.

Immediately after the intravenous injection of 2 ml. of mercury one of the dogs became apneic and required respiratory assistance for two hours before spontaneous respiration was resumed. The remaining dogs showed no clinical evidence of acute pulmonary embolism. X-rays taken 5 to 35 minutes after injection demonstrated rather large (0.5 to 2.0 mm.) mercury globules in the superior vena cava, intercostal vessels, and inferior vena cava. Smaller amounts were present in the pulmonary vessels (Fig. 3*A*). The X-rays were repeated 7, 14, 21, and 28 days after the injection. During the period of follow-up, particle size decreased and discrete spherical globules were less common. The mercury moved out of the larger venous channels. There was a heavier concentration in the lung fields (Fig. 3*B*). Mercury drop-

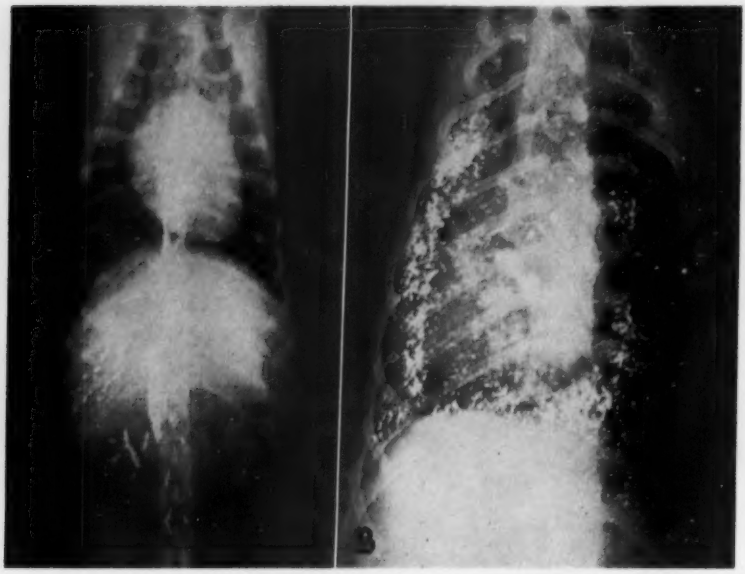


Fig. 3.—Anteroposterior roentgenograms taken of dogs following the intravenous injection of 2 ml. of metallic mercury. *A*, 15 minutes following injection. *B*, 21 days following injection.

lets were not seen in the heart, liver, spleen, or kidneys of the living animals. Three of the six dogs died during the 28-day period of observation. The survivors developed marked emaciation during this period.

In those animals killed at 28 days or less, the lungs were extensively involved with firm, yellowish, miliary nodules (0.5×0.5 cm.) containing mercury droplets. Similar nodules were found in the livers and spleens of four animals. Similar lesions occurred along the anterior descending branch of the left coronary artery, with extensive involvement of the anterior wall of the right ventricle, in two dogs. No gross changes were found in the kidneys. Metallic mercury was seen in the intercostal veins. None was found in the paravertebral venous plexus. X-rays of the removed organs showed mercury droplets in the liver, spleen, and heart. These were not demonstrable by x-ray in the living animals.

The microscopic pathology of the nodules in the lungs, liver, spleen, and myocardium was similar. Basically, they were subacute and chronic miliary abscesses. The abscesses usually contained a central spherical metallic particle surrounded by a dense zone consisting of polymorphonuclear leukocytes. A dense aggregate of macrophages surrounded the polymorphonuclear zone. The entire process was encircled by a zone of active fibroblastic and capillary proliferation (Fig. 4). There were small focal hemorrhages and hemosiderin deposits adjacent to the inflammatory reaction. None of the lesions contained foreign-body giant cells. In addition, purulent bronchitis with bronchiectasis and squamous metaplasia of the bronchial epithelium was noted in the lungs. The renal tubules showed suggestion of recent tubular regeneration.

The urine from one of this group of animals contained 3γ of mercury at the time they were killed (28 days).

The single animal which was kept for six months (200 days) following the intravenous injection of mercury did quite poorly. At the time it was killed, marked emaciation was apparent, but weight loss had not occurred. X-rays revealed mercury particles in both lung fields throughout the period. A decrease in the quantity of mercury present was not evident. At the time the animal was killed, firm yellowish miliary nodules containing mercury droplets were seen in the lung parenchyma, particularly in the basilar segments, and in the myocardium, again along the anterior descending branch of the left coronary artery. No other miliary nodules were noted. Other significant findings included pleural and pleuropericardial adhesions and hypertrophy of the right ventricle. The microscopic pathology of the nodules was basically similar to that noted at one month. The zone surrounding the metallic particle still consisted of a dense aggregation of polymorphonuclear

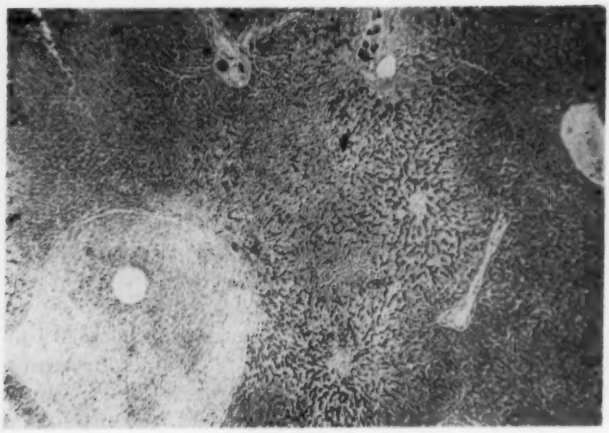
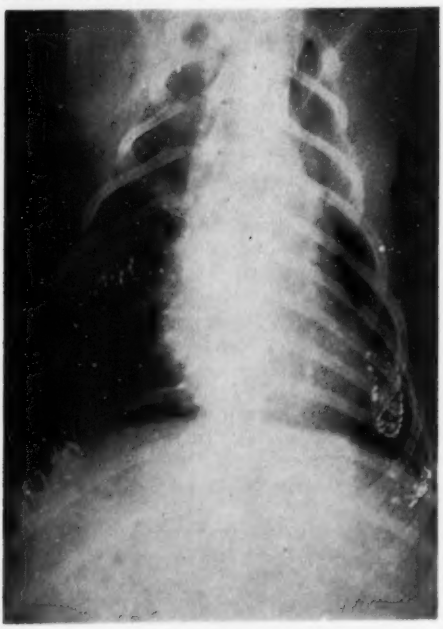


Fig. 4.—Photomicrograph of a typical miliary abscess in the liver of a dog killed 28 days after the intravenous injection of 2 ml. of metallic mercury; ×35.

leukocytes. The only progression noted was the development of an outer dense fibrous layer.

A single animal was given a subcutaneous injection of approximately 2 ml. of mercury. The forearm became warm, reddened, and swollen within 72 hours. At seven days multiple purulent, draining sinuses developed from which metallic mercury could be extruded. The sinuses persisted until the time the animal was killed, at 28 days. X-rays showed mercury in the tissues. No systemic mercury was demonstrated. The skin and subcutaneous tissue was thickened and granular. No other gross changes were noted at autopsy. Microscopically, multiple subacute and chronic dermal abscesses similar to the visceral lesions following intravenous injection were noted.

Fig. 5.—Anteroposterior roentgenogram taken of a dog 14 days following the endotracheal administration of 2 ml. of metallic mercury.



The administration of 2 ml. of mercury through an endotracheal tube had no apparent effects, other than stimulating a cough response. The immediate postinoculation x-rays revealed a diffuse alveolar spread. Less mercury was present in x-rays at 7 and 21 days. The mercury droplets settled to the basal segments of the pulmonary lobes (Fig. 5). Mercury droplets could not be seen elsewhere in the body.

At autopsy, firm yellowish nodules (0.5×0.5 mm.) containing mercury droplets were noted in the basal portion of the lower and middle lobes. No gross lesions were noted in other organs. Microscopically, the lesions were subpleural abscesses with the same characteristic structure as noted with other routes of administration.

No mercury could be detected by quantitative chemical analysis of feces or urine at the time the animal was killed.

Comment

In a similar case reported by Umber, 2 ml. of metallic mercury was injected intravenously in a suicide attempt.[14] The patient remained asymptomatic for four days. She then noted palpitation, followed by right thoracic pain, diarrhea, tenesmus, and stomatitis. These symptoms lasted eight days. Abdominal pain persisted for approximately eight weeks. Small paravenous abscesses developed at the site of injection. Mercury

droplets were obtained upon incision of the abscesses. Konig subsequently published a follow-up report on this patient.[9] She died four years later with "pulmonary tuberculosis"; however, no bacterial confirmation was cited. Droplets of mercury ranging from several microns to several hundred microns were demonstrated in the lungs, kidneys, heart, spleen, and colon at autopsy. The larger particles were encapsulated by connective tissue in a mild foreign-body reaction.

Our patient initially presented chest pain, cough, fever, and dyspnea, acute symptoms which suggested either pulmonary embolism or pneumonia. There was marked impairment of vital capacity. Laboratory studies revealed a leukocytosis, elevated sedimentation rate, albuminuria, hyperglobulinemia, and sulfobromophthalein retention. Eight days after admission he was asymptomatic and laboratory findings were normal, except for a decreased vital capacity and maximum breathing capacity. Five weeks later a nodule developed in his left antecubital fossa which contained metallic mercury. The patient denied self-inoculation of mercury. However, he suggested he might have aspirated mercury eight months prior to his acute symptoms. A normal chest x-ray and upper gastrointestinal series during this interval and the demonstration in animals that the pattern of distribution was that of intravenous administration were difficult to reconcile with denial of intravenous self-inoculation.

Metallic mercury has been felt to produce bland embolization.[4,15] However, miliary abscesses of a characteristic nature developed in the lungs, liver, spleen, and myocardium in our experimental studies. The presence of lesions in the coronary arteries demonstrates that metallic mercury is able to pass through the pulmonary capillary circulation. The chronicity of the marked tissue reaction produced by mercury causes concern regarding the ultimate prognosis in this case, even though there is no evidence of pulmonary, renal, hepatic, or cardiac damage at this time.

Summary

An instance of the intravenous self-administration of metallic mercury is described, which presented as acute pulmonary embolization with associated transient evidence of renal and hepatic impairment.

The experimental administration of metallic mercury intravenously, endotracheally, or subcutaneously into dogs resulted in typical abscesses. The intravenous inoculation produced widespread miliary lesions in the lung, liver, spleen, and myocardium. The lesions remained localized, and systemic distribution was not noted following the endotracheal or subcutaneous administration.

Col. E. B. Litteral, Chief of the Neuropsychiatric Service, provided the opportunity of evaluating the patient, Dr. L. R. Goldbaum performed the quantitative mercury determinations, and Sfc. W. Holder assisted with the experimental x-rays.

Walter Reed Army Hospital, Washington 12, D. C.

REFERENCES

1. Birnbaum, W.: Inflammation of Vermiform Appendix by Metallic Mercury, Am. J. Surg. 74:494, 1947.

2. Campbell, J. S.: Acute Mercurial Poisoning by Inhalation of Metallic Vapour in an Infant, Canad. M. A. J. 58:72, 1948.

3. Cantor, M. O.: Mercury Lost in the Gastrointestinal Tract: Report of Unusual Case J. A. M. A. 146:560, 1951.

4. Cohn, B.: Klinik der embolischen Gefässkrankheiten, Berlin 266:1860.

5. Dujadin-Beaumetz, G.: Diseases of Stomach and Intestines, Baltimore, William Wood & Company, 1886.

6. Giese, A. C.: Mercury Poisoning, Science 91:476, 1940.

7. Goodman, L. S., and Gilman, A.: The Pharmacological Basis of Therapeutics: A Textbook of Pharmacology, Toxicology, and Therapeutics for Physicians and Medical Students, Ed. 2, New York, The Macmillan Company, 1955, p. 973.

8. Holzback, E.: Quecksilbergranulom der Haut, Arch. path. Anat. 314:287, 1947.

9. Konig, E.: Über Quecksilber in Wunden, Chirug 11:57, 1939.

10. Lathem, W.; Lesser, G. T.; Messinger, W. J., and Galdston, M.: Peripheral Embolism by Metallic Mercury During Arterial Blood Sampling: Report of 2 Cases, A. M. A. Arch. Int. Med. 93:550, 1954.

11. Lindemuth, W. W.: Fecal Fistula Due to Metallic Mercury from Miller-Abbott Tube: Report of Case, J. A. M. A. 141:986, 1949.

12. Sitson, quoted by Umber.[14]

13. Stammel, C.: Metallic Mercury in Subcutaneous Tissue, Mil. Surgeon 65:529, 1929.

14. Umber, F.: Quecksilber-Embolien der lebenden Lunge durch intravenöse Injektion von metallischen Quecksilber, Med. Klin. 19:35, 1923.

15. Van Allen, C. M.; Nocoll, G. I., and Tuttle, W. M.: Lung Changes After Occlusion of Pulmonary Artery Branches by Embolism and by Ligature, Yale J. Biol. & Med. 2:363, 1929.

16. Zwinger, T.: Mercuri crudi effectus in colic a spasmodica a fecum duritie alvum contumacitur obstruente oriusida, Coll. Acad. mem. 7:488, 1766.

Influence of Promazine and Methylphenidate on Cerebral Hemodynamics and Metabolism

WILFRED R. EHRMANTRAUT, M.D.; JAMES G. SHEA, M.D.; HOWARD E. TICKTIN, M.D., and JOSEPH F. FAZEKAS, M.D., Washington, D. C.

Promazine, a new phenothiazine derivative, appears to offer considerable promise in the control of patients with increased psychomotor activity [1,2] as well as assisting in the management of patients with various medical emergencies.[3] The exact physiological mechanism by which this drug exerts its effects is not known; however, previous studies [4] have shown chlorpromazine, a somewhat similar phenothiazine derivative, to have no demonstrable effects upon total cerebral hemodynamics and oxygen utilization. It was nevertheless considered worth while to determine whether this was also true of promazine. In addition, this study afforded the opportunity to examine the clinical and quantitative cerebral effects of methylphenidate hydrochloride (an analeptic drug) alone and upon subjects to whom promazine had been previously administered.

Methods

The subjects of the present study were 21 hospital patients who had been admitted for a variety of acute illnesses but were convalescent and otherwise in reasonably good condition. They were divided into three groups; the first group, of 12 patients, was given from 50 to 200 mg. of promazine intravenously. The second group consisted of seven subjects, who received from 10 to 40 mg. of methylphenidate hydrochloride intravenously, and the third group comprised nine subjects, who were first given 75 to 200 mg. of promazine intravenously, followed within 20 to 60 minutes by an intravenous injection of from 10 to 20 mg. of methylphenidate hydrochloride. In all subjects, control observations of hemodynamics and metabolism were made immediately and repeated within 30 minutes after the injection of the drug. Scheinberg and Stead's modification [6] of Kety and Schmidt's procedure [5] for the determination of cerebral blood flow was applied in this study. The gas mixtures utilized were those described by Kety and Schmidt.[5] The oxygen content of the blood was determined by the manometric technique of Van Slyke and Neill.[7] Mean arterial blood pressure (MAP) was obtained directly from the femoral artery by means of a damped aneroid manometer.[8]

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From the George Washington and Georgetown University Medical Divisions, District of Columbia General Hospital.

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The promazine (Sparine) used in this study was supplied by Wyeth Laboratories, Inc., Philadelphia. The methylphenidate hydrochloride (Ritalin) used in this study was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Results

In Table 1, the effects of promazine alone on cerebral hemodynamics and metabolism are compared with values obtained immediately before drug administration. There was no statistically significant change in any of the cerebral functions after doses of promazine ranging from 50 to 200 mg. Mean values for arterial pressure were also essentially unchanged.

In Table 2, the results of cerebral studies before and after the administration of methylphenidate hydrochloride are presented. The data failed to disclose any statistically significant changes in cerebral function or arterial pressure following administration of this drug.

The findings in patients given both promazine and methylphenidate hydrochloride are presented in Table 3. Methylphenidate hydrochloride did not have any demonstrable

TABLE 1.—*The Effects of Promazine on Cerebral Hemodynamics and Oxygen Utilization* *

Subj.	Age	CBF		CMRO$_2$		CVR		CAVO$_2$		MAP		Promazine, Mg.
		C	E	C	E	C	E	C	E	C	E	
1	51	44.3	35.6	1.8	1.9	1.3	1.7	4.12	5.36	56	59	200
2	32	51.7	41.3	3.4	2.9	1.8	2.5	6.49	7.14	94	102	200
3	76	28.2	27.2	2.1	2.4	2.7	2.8	7.35	8.64	75	77	125
4	28	49.0	51.2	2.6	2.6	1.6	1.2	5.36	4.27	76	74	50
5	36	58.5	54.2	2.5	2.4	1.5	1.5	4.28	4.51	87	79	100
6	35	82.7	51.8	3.0	2.7	1.0	1.4	3.68	5.29	85	70	100
7	50	51.4	32.3	2.8	2.2	1.6	2.4	5.43	6.81	84	79	150
8	58	54.2	43.5	2.3	2.1	1.6	1.6	4.23	4.94	85	70	100
9	22	67.9	47.6	3.3	2.8	1.2	1.7	4.83	5.98	83	82	150
10	45	66.1	52.4	3.0	3.2	1.9	2.1	4.61	6.09	127	110	100
11	51	75.2	64.0	2.7	2.3	1.1	1.0	3.60	3.57	80	64	75
12	45	45.8	56.7	1.9	1.9	1.9	1.4	4.07	3.30	86	77	100
Means	44	56.2	47.3	2.6	2.4	1.6	1.8	4.84	5.49	85	79	121

* CBF indicates cerebral blood flow in cubic centimeters/minute/100 gm. of brain; CMRO$_2$, cerebral oxygen consumption in cubic centimeters/minute/100 gm. of brain; CVR, cerebral vascular resistance in millimeters of Hg/cubic centimeter of blood/minute/100 gm. of brain; CAVO$_2$, cerebral arteriovenous oxygen difference in volumes per cent; MAP, mean arterial blood pressure in millimeters of Hg; C, control; E, experimental.

effect on cerebral functions, even though varying degrees of clinical reversal of the central depressing effect of promazine were apparent in these cases.

Comment

The results indicate that promazine, like chlorpromazine, has no measurable effect upon either total cerebral blood flow or measurable oxygen consumption. It appears probable that metabolic changes attendant upon its administration are extremely slight or are localized to central nervous system areas so small that the over-all values for these cerebral functions are not appreciably altered. Recent in vitro studies [9] indicate that promazine inhibits both cytochrome oxidase and adenosine triphosphatase. Inhibition of the latter enzyme system which is concerned primarily with dephosphorylization of high-energy phosphate compounds need not necessarily be associated with changes in cerebral oxygen utilization. The failure of methylphenidate hydrochloride to alter significantly total cerebral oxygen utilization may perhaps be attributed to the inadequacies of the method employed. It is also probable, however, that oxidative reactions may not be influenced by methylphenidate hydrochloride and that its pharmacological antagonism may result from the breakdown of high-energy compounds.

Methylphenidate hydrochloride was, however, clinically effective in reversing the sedative action of promazine. In 19 subjects with various disturbances characterized by increased psychomotor activity, methylphenidate hydrochloride was administered intravenously in doses ranging from 10 to 30 mg. after sedation had been achieved by doses of promazine between 75 to 750 mg. In general the clinical response to the administration of methylphenidate hydrochloride consisted in the appearance of increased alertness, freer verbalization, or improved articulation. In most subjects there was almost immediate partial or complete return of increased abnormal psychomotor activity

TABLE 2.—*The Effects of Methylphenidate Hydrochloride on Cerebral Hemodynamics and Oxygen Utilization* *

Subj.	Age	CBF		CMRO$_2$		CVR		CAVO$_2$		MAP		Methylphenidate, Mg.
		C	E	C	E	C	E	C	E	C	E	
1	76	28.2	35.9	2.1	2.7	2.7	2.3	7.35	7.41	75	84	10
2	56	44.8	37.7	2.7	2.2	2.1	2.3	5.93	5.90	94	87	10
3	82	53.7	39.9	2.7	2.6	1.9	2.6	5.01	6.50	103	104	40
4	16	44.9	44.5	4.0	4.0	2.5	2.8	8.84	8.98	112	125	20
5	45	50.0	47.9	3.6	3.3	2.0	2.2	7.25	6.98	102	105	20
6	49	56.2	53.9	3.5	3.0	1.9	2.0	6.22	5.63	104	110	20
7	53	52.9	49.7	2.7	3.2	2.0	2.2	5.17	6.41	108	110	30
Means	54	47.2	44.2	3.0	3.0	2.2	2.3	6.54	6.83	100	104	21

* See Table 1 for explanation of abbreviations.

TABLE 3.—*The Effects of Promazine and Methylphenidate Hydrochloride on Cerebral Hemodynamics and Oxygen Utilization*

Subj.	Age	CBF			$CMRO_2$			CVR			$CAVO_2$			MAP			Promazine, Mg.	Methylphenidate, Mg.
		C	P	R	C	P	R	C	P	R	C	P	R	C	P	R		
1	22	67.9	47.8	49.3	3.3	2.8	3.3	1.2	1.7	1.6	4.83	5.98	6.72	83	82	80	150	10
2	50	51.4	32.3	38.4	2.8	2.2	2.5	1.6	2.4	1.7	5.43	6.81	6.62	84	79	67	150	20
3	36	58.4	54.2	51.6	2.5	2.4	3.5	1.5	1.5	1.3	4.28	4.51	6.81	87	79	65	100	10
4	51	44.3	35.6	37.9	1.8	1.9	1.8	1.3	1.7	1.5	4.12	5.36	4.87	86	89	55	200	10
5	45	45.8	56.7	50.8	1.9	1.9	1.8	1.9	1.4	1.6	4.07	3.30	3.52	86	77	83	100	10
6	76	28.2	27.2	32.6	2.1	2.4	3.0	2.7	2.8	2.3	7.35	8.64	9.14	73	77	73	125	10
7	28		41.5	40.5		2.4	2.4		2.0	1.6		5.84	5.89		83	65	200	10
8	43		44.1	47.8		2.8	2.8		2.4	2.4		6.41	5.95		104	115	100	10
9	42		78.4	65.1		1.4	1.2		0.8	1.1		1.73	1.83		64	69	100	10
Means	44	49.3	46.4	46.0	2.4	2.2	2.5	1.7	1.9	1.7	5.01	5.40	5.71	78	78	75	136	11

* See Table 1 for explanation of abbreviations.

or tremor which had been suppressed by promazine. The net impression was that methylphenidate hydrochloride clinically was able to effect a definite reversal of the subcortical depression induced by promazine. This activation of the alerting mechanism by methylphenidate hydrochloride as well as its analeptic action in patients receiving small doses of barbiturates [10] would seem to suggest that the drug stimulates both cortical and subcortical centers. These observations suggest its usefulness as an antidote to central nervous system depression inadvertently induced by phenothiazine derivatives.

Summary and Conclusions

The effects of promazine and methylphenidate hydrochloride, administered separately or in combination, upon cerebral hemodynamics and metabolism were determined in 21 patients. Neither drug significantly altered measurable cerebral oxygen consumption or hemodynamics. The clinically apparent subcortical depressant effect of promazine was reversed by the administration of methylphenidate hydrochloride. It is suggested that the analeptic activity of the latter drug may be due to stimulation of both subcortical and cortical centers, and that it may be used to combat central nervous system depression inadvertently induced by phenothiazine derivatives.

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District of Columbia General Hospital, 19th & E Sts., S. E. (3) (Dr. Fazekas).

REFERENCES

1. Fazekas, J. F.; Schultz, J. D.; Sullivan, P. D., and Shea, J. G.: Management of Acutely Disturbed Patients with Promazine (Sparine), J. A. M. A. 16:46, 1956.

2. Mitchell, E. H.: Treatment of Acute Alcoholism with Promazine (Sparine), J. A. M. A. 16:44, 1956.

3. Shea, J. G.; Ehrmantraut, W. R.; Ticktin, H. E.; Sullivan, P. D., and Fazekas, J. F.: Use of Promazine in the Management of Medical Emergencies, Mil. Med., to be published.

4. Fazekas, J. F.; Albert, S. N., and Alman, R. W.: Influence of Chlorpromazine and Alcohol

on Cerebral Hemodynamics and Metabolism, Am. J. M. Sc. 230:128, 1955.

5. Scheinberg, P., and Stead, E. A., Jr.: The Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization, and Peripheral Resistance, with Observations on Effect of Tilting and Anxiety, J. Clin. Invest. 28:1163, 1949.

6. Kety, S. S., and Schmidt, C. F.: The Nitrous Oxide Method for the Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Invest. 27: 476, 1948.

7. Peters, J. P., and Van Slyke, D. D.: Quantitative Clinical Chemistry: Methods, Baltimore, Williams & Wilkins Company, 1932, p. 321.

8. Alman, R. W., and Fazekas, J. F.: Apparatus for Continuous Blood-Pressure Observation, New England J. Med. 248:105, 1953.

9. Bernsohn, J.; Namajuska, I., and Cochrane, L. S. G.: Inhibition of Brain Cytochrome Oxidase and ATP-ase by Chlorpromazine Analogues, Proc. Soc. Exper. Biol. & Med. 92:201, 1956.

10. Fazekas, J. F.: Unpublished data.

Dermatomyositis

A Review of Nineteen Cases in Adolescents and Children

MARK ALLEN EVERETT, M.D., Oklahoma City, and ARTHUR C. CURTIS, M.D., Ann Arbor, Mich.

Introduction

The purpose of this paper was to review the course of dermatomyositis in 19 adolescents and children seen at the University of Michigan Hospital between 1935 and 1955. The effects of corticotropin (ACTH) and cortisone therapy were assessed. Several previously unemphasized clinical aspects were noted and the pathological picture assayed.

Review

Dermatomyositis is a disease of infrequent occurrence characterized by insidious onset, nonsuppurative inflammation of striated muscles, and death in about one-half of the cases. Although several hundred case reports of this disease have been published since dermatomyositis was described by Wagner, in 1863, most reports are of only one or a few cases. Reviews of the literature have been accomplished by several authors,* including Karelitz and Welt,[1] in 1932; Stuckey,[2] in 1935; Keller,[3] in 1936, and most completely by Schuermann,[4] who in 1939 reviewed 263 case reports among which were 47 children. Selander,[5] in 1950, compiled 22 cases of dematomyositis in children with a review of the pathological specimens in these cases. Most of these patients were German, English, or Dutch. Only four large series of patients from one clinical unit exist. These are the O'Leary and Waisman series from Mayo's (1940),[6] the Sheard series from Presbyterian Hospital (1951),[7] and the Dowling series from St. Thomas' Hospital (1955).[8] A series in children seen at the Boston Children's Medical Center was presented by Wedgwood, Cook, and Cohen, in 1953.[9]

The occurrence of coexistent malignancy was first noted by Bezecny,[10] in 1935, and one or two cases have been reported by several authors. These were all reviewed by Dowling, in 1955.[8] The largest series was reported by Curtis, Blaylock, and Harrell,[11] in 1952, where 8 malignancies in a series of 45 afflicted patients were reported. All eight patients were adults. Three lesions were carcinomas of breast or cervix. The other lesions were cases of Hodgkin's disease, multiple myeloma, a parotid carcinoma, and two sarcomas.

Clinical Material

An unequivocal diagnosis of dermatomyositis was made in 60 persons at the University of Michigan Hospital during the past 20 years (1935-1955). Of these, 41 (68.4%) were greater than 23 years of age at the onset of the disease. Nineteen (31.6%) were between the ages of 4 months and 17 years. This report evaluates the outcome in this latter younger group (Table 1) of 19 cases, all of whom were followed to either death or the present date. The longest period of observation was 19 years in one instance, and the shortest period of observation was two years. Eighteen of the cases were white children, and one was a Negro. Seven were males, and twelve were females. Of the total group, today 11 are dead and 8 are living. There was a 100% follow-up of these patients.

Initial Symptom

The initial symptom (Table 2) was facial erythema in six of the patients. This erythema was frequently over the malar areas and bridge of the nose ("butterfly

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Department of Dermatology, University of Michigan Hospital and Medical School.

* Recently a statistical survey of 270 cases has been made at the Mayo Clinic.[12]

TABLE 1.—*Summary of Cases of Dermatomyositis*

Case	Age at Onset, Yr.	Sex	Biopsy	Facial Erythema	Grouped Muscle Weakness	Periorbital Edema	Pain in Muscles	Low-Grade Fever	Induration	Contractures	Poikiloderma	Calcinosis	Gastrointestinal Involvement	Cardiorespiratory Involvement	Hepatomegaly	Arthralgia	Present Status of Patient	Age at Death or at Present, Yr.	Cause of Death
1	14-6/12	M	+	+	+	+	+	+	+	+	+	+	+	+			Dead	15-5/12	Respiratory
2	4	F															Dead	11	Hemorrhage
3	0-5/12	F															Dead	12	Respiratory
4	4	M	+	+	+	+	+	+	+	+	+	+			+		Active	11	
5	11	F	+	+	+	+	+	+	+	+	+	+			+		Active	34	
6	6	M	+	+	+	+	+	+	+	+	+	+	+	+	+		Partially active	19	
7	17-10/12	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	9	"Dermatomyositis"
8	6	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	18-4/12	Cardiac
9	2-6/12	M	+	+	+	+	+	+	+	+	+	+	+	+	+		Active	13	
10	17	M	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	3-6/12	Cardiorespiratory
11	5	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	10	Hemorrhage, cardiac
12	10	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	18	Cardiorespiratory
13	3	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	6	Cardiac
14	14	M	+	+	+	+	+	+	+	+	+	+	+	+	+		Active	28	
15	17	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Active	8	
16	12	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	22	Calcific pericarditis
17	11	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Bedridden	26	
18	12	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Dead	14	Septicemia
19	11	F	+	+	+	+	+	+	+	+	+	+	+	+	+		Active	27	

area") and in most instances (five) extended up over both orbital ridges to the eyebrows and temple. The color was described as violaceous, magenta, or heliotrope, thus differing in shade from the erythema of the usual case of lupus erythematosus. In four the onset was characterized by fatigue and in three by specific muscle weakness. Six had miscellaneous findings. This frequency of initial findings agrees with the consensus of the other large series.[6-9]

Physical Findings

The physical findings on these patients are tabulated in Table 3. Findings included are not limited to those found at the first examination. It is of interest that temperature greater than 100.5 F was not seen except in the presence of an infection. Furthermore, demonstrable generalized muscular weakness, arthritis, or arthralgia were notable by their complete absence from this series. None of these children had or has a malignant growth, although 8 malignancies occurred among the 40 older patients at this hospital. Two of the patients had induration and vascular phenomena suggestive of scleroderma after the initial acute phases of the disease.

Historical Findings

Historical findings of interest included seven patients (37%) who stated that their disease was definitely aggravated by sunlight. Five gave an atopic family history, and three had the prior administration of sulfonamides (two) or penicillin (one). In only one, however, did the onset of disease seem related to the drug administration (Case 11). In this case the disease was immediately preceded by a generalized maculopapular and erythematous eruption coincident with ingestion of a sulfonamide.

Laboratory Findings

Other than increased urinary creatine (reflecting the catabolism of skeletal muscle), the laboratory findings in dermatomyositis are not remarkable. The Kahn tests were

all negative. The sedimentation rate was elevated in 7 of the 19 patients. Low-normal hemoglobins were frequently encountered. LE cell tests were repeatedly negative in the six patients in whom they were performed. The white cell counts ranged between 5200 and 11,400 in the absence of demonstrable infection. Eosinophilia of 5%-11% was encountered in 6 of the 19 children. Urinary studies other than creatine were within normal limits. Serum electrolytes were normal except in those patients receiving high doses of corticotropin or cortisone. Gastrointestinal bleeding was detected in three patients, one of whom was being given intensive steroid therapy. The degree of activity of the disease seemed best reflected in the sedimentation rate, and by the pulse rate in those with cardiac involvement.

TABLE 2.—*Original Symptom or Sign in Nineteen Cases of Dermatomyositis*

Symptom	No.	Per Cent
Facial erythema	6	31.6
Fatigue	4	24.2
Weakness (specific)	3	15.8
Muscle tenderness	2	10.5
Erythema elsewhere	1	5.3
"Sunburn"	1	5.3
"Drug eruption"	1	5.3
Raynaud's phenomenon	1	5.3

X-Ray Findings

The major roentgenographic changes were of some diagnostic aid. Six of the nineteen patients had involvement of the muscles of deglutition with hypopharyngeal paralysis of varying degrees. This could be demonstrated with barium swallows in which a resultant regurgitation of the barium would occur. The involvement of the hypopharyngeal musculature with subsequent abnormality of deglutition is of probable prognostic value, as five of the six patients with such involvement died of their disease. One patient showed obliteration of the rugal pattern and rapid peristalsis in the duodenum which was present throughout the activity of the disease. Nonspecific changes included cardiac enlargement and pulmonary inflammatory changes in occasional patients. Later, during the development of the disease, tissue calcification may occur and was demonstrated by x-ray in six of our patients. It should be noted that the major precursors of calcinosis universalis are dermatomyositis and scleroderma, as was shown by Wheeler et al.[12]

TABLE 3.—*Physical Findings in Nineteen Cases of Dermatomyositis*

Finding	No.	Per Cent
Grouped muscle weakness	19	100
Fatigue	18	94.7
Periorbital erythema	17	89.5
Periorbital edema	17	89.5
Extensor erythema	16	84.4
Pain in muscles	15	79.5
Low-grade fever	14	73.7
Tissue induration	12	63.2
Contractures	12	63.2
Poikiloderma	11	57.9
Calcinosis	8	42.4
Cardiovascular involvement	6	31.6
Gastrointestinal involvement	6	31.6
Hepatomegaly	4	24.2
Alopecia	3	15.8
Arthralgia or arthritis	0	0
Tumors (malignant)	0	0

Pathological Findings

In this series of patients there were 47 specimens of skin, subcutaneous tissue, and muscle (Table 4). Two patients had no biopsy, and two showed no significant pathologic changes. In those with abnormal findings in skeletal muscle, most earlier biopsies

TABLE 4.—*Pathological Findings of Forty-Seven Biopsy Specimens in Seventeen Patients with Dermatomyositis*

Epidermis	
Hyperkeratosis	2
Atrophy	3
Corium	
Calcium deposits	4
Periappendiceal infiltrate	4
Perivascular round cell infiltrate	2
Round-cell infiltrate	1
Edema	2
Collagen degeneration	2
Negative	5
Fat	
Necrosis, focal	1
Skeletal muscle	
Atrophy	3
Focal atrophy	3
Focal necrosis	2
Zenker's necrosis	3
Increased muscle nuclei	2
Decreased muscle nuclei	1
Perivascular infiltrate (round cell)	9
Proliferative arteritis	1
General round-cell infiltrate	1
Fibrosis	1
Normal	5

TABLE 5.—*Treatment of Dermatomyositis*

Treatment Schedule	Total Treated	Objectively Improved	Subjectively Improved	No Change	Died
PABA daily	4	0	1	3	2
Corticotropin, 160–1,000 mg. and/or hydrocortisone, 100–800 mg., q.i.d.	5	0	2	3	3
Corticotropin, <160 mg./day, and/or hydrocortisone, <100 mg. q.i.d.	3	0	1	2	1
Vitamin E, 50 mg. q.i.d.	2	0	0	2	1

showed a mild to moderate perivascular infiltrate with variable increases in muscle nuclei. As the disease progressed the increase in interstitial nuclei was greater. A few showed heavy lymphocytic invasion of muscle. Numerous areas of circumscribed muscle fiber atrophy or degeneration were seen. This was described as "Zenker's necrosis" in a few. Several patients showed a loss of muscle architecture without necrosis. Hemorrhage was present in four biopsy specimens.

After the passage of time, the infiltrative features were minimal to absent and areas of fibrosis were prominent. Calcium deposits later appeared in one-third of the cases. Proliferative, obliterative, or necrotic vascular changes were seen in only one biopsy specimen. In conclusion, pathological changes in muscle, although usual, were not universally present in even clinically involved muscle. When present they tended to be (1) focal, (2) inflammatory in nature, (3) proceeding to necrosis, fibrosis, and often calcification, and (4) unaccompanied by vasculitis. The invariable lack of involvement of vessel walls bears out the observations of the other well-documented series.[3,5-7,9]

Postmortem studies in six patients revealed pathologic involvement of cardiac and/or pharyngeal muscles similar to that described under skeletal muscle. Ulceration and hemorrhage of the gastrointestinal tract were found in two cases without accompanying obliterative vascular changes. Calcinosis was described in three cases, including one of calcific pericarditis. Other than pulmonary infections involvement of other organ systems was not found.

Epidermal and dermal changes were seen in about one-half of the cases. Mostly these reflected areas of poikiloderma, i. e., atrophy, telangiectasia, hydroptic degeneration of basal cells, hyperkeratosis, hyperpigmentation, and minimal infiltrate. Perivascular and periappendegeal infiltrates were mild and present in only a few cases. Edema and collagenous changes were seen in two patients. These latter changes are nonspecific.

Therapy

Specific therapy (Table 5) utilized in these patients included *p*-aminobenzoic acid (PABA), corticotropin, cortisone and its derivatives, and vitamin E. Numerous nonspecific medications were used. Five patients were started on PABA. One did not tolerate the drug, and four had three months to several years of treatment. Of these four people, one attributed remission of her calcinosis to treatment, but in three there was no effect from PABA; two of the four patients died. Thus a beneficial effect of PABA administration was not demonstrable in this series. Eight patients were treated with corticotropin and/or cortisone derivatives. Five of these eight patients had what can be considered an adequate trial of therapy. Of these five none had demonstrable objective improvement other than temporary suppression of fever and erythema proportional to the magnitude and duration of dosage. Only two subjectively improved, and one of these died. Four of the eight patients in this treatment group are now

TABLE 6.—*Cause of Death in Eleven of Nineteen Cases of Dermatomyositis*

Bronchopneumonia with dermatomyositis	5
Cardiac failure with dermatomyositis	3
Hemorrhage with dermatomyositis	2
Calcific pericarditis	1

TABLE 7.—*Present Status of Nineteen Patients with Dermatomyositis*

Dead	11
Living	8
Completely active with few residua	4
Partially active	2
Confined to bed (contractures)	2
Disease quiescent	8

dead. It is our feeling that corticotropin and/or cortisone derivatives provide a feeling of well-being and suppress inflammatory signs in some patients but that these drugs do not alter the basic course or outcome of the disease. Small doses of vitamin E likewise failed to result in improvement.

All patients who did not die early in the course of the disease had physical therapy to prevent or correct contracture deformities. It appears that early adequate physical measures, such as exercise, heat, and splinting, played a major role in the prevention of crippling deformities. Those patients with marked contractures were patients who failed to have early orthopedic care. In the patients who survived the acute phases of the disease the single most important treatment factor appeared to be the use of physical medicine to prevent contractures.

Course

Eleven of the nineteen patients have died. Of these, four died within the first year because of hypopharyngeal paralysis and/or cardiac involvement. Those dying after the first year succumbed to infectious processes, chiefly pneumonia. The occurrence of this complication has been no less frequent in the antibiotic era. This is probably due primarily to mechanical factors. One patient died of calcific pericarditis. Thus it appears that involvement of vital structures, the heart and the hypopharynx, is the cause of death in the first few months of the disease, while later these patients seem particularly susceptible to mortal infections, especially bronchopneumonia, which fail to respond to antibiotics.

Of those eight who survived, only one had detectible progression or activity of his dermatomyositis after three years. Four of these patients are completely active and either have only minimal to moderate fibrosis about some joints or insignificant residual pigmentary changes. One has residual calcinosis about some of the joints. The other four patients all have had severe calcinosis, and two are now partially active and two confined to bed because of contractures and fibrosis of the extremities. It would seem that crippling residua of the disease are more likely to obtain in those patients with calcinosis universalis.

Conclusions

The experience with these 19 adolescents and children would indicate that of those who develop dermatomyositis, about 20% will be dead of the disease within the first year. An additional 30%-40% will die from intercurrent infection within the first four or five years. Of the approximately 40% who survive, nearly all will have inactive disease within the first two years. About one-fourth of the survivors, or 10% of the total, will have residua of such severity as to confine them to bed; another one-fourth, or 10%, will be severely restricted as to activity on account of contractures or muscular fibrosis and dermal induration. About 20% of the total will return to full activity with minimal or no residual signs.

The incidence of remissions and exacerbations was nil in this series. Once inactive the disease remained inactive. No therapy seemed to have influenced favorably the outcome of the disease, although steroids in large doses tended to suppress the indications of active inflammation and on occasion led to a feeling of well-being. It is noteworthy that none of these patients had

TABLE 8.—*Residual Findings in Dermatomyositis (Eight Living Patients)*

No cutaneous lesions	2
Poikiloderma	3
Calcinosis	3
Induration	4
Contractures	
Moderate	2
Severe	3
Mild limitation of joint motion	1
Muscle weakness (specific)	2
Muscle wasting (specific)	6

joint involvement or arthralgia at any time during their illness, although ankylosis from periarticular fibrosis was not uncommon. The infrequency of true joint symptoms was a finding of the other major series. Most of the patients benefited from physical medicine and orthopedic measures; those patients in whom such measures were delayed showed a higher incidence of contractures and disabling sequelae. None of these patients had an associated malignancy.

It would appear that dermatomyositis is a clinical entity which obtains its integrity from its unique clinical picture and rather typical course, eventuating in death, arrest, or recovery usually in 3 to 36 months. Although the histopathological features are frequently not diagnostic, the prominence of atrophy, necrosis, homogenization, and degeneration of skeletal muscle fibers is suggestive, particularly when accompanied by moderate inflammatory changes. The absence of necrotic, proliferative, or occlusive changes in the vascular walls and the absence of a positive LE-cell phenomenon is a persistent observation in the major reported series of dermatomyositis. Unfortunately the appellation "collagen disease" has obscured the essential uniqueness of this disorder. Admittedly most careful studies indicate occasional points of clinical similarity between some cases of dermatomyositis and scleroderma. With the increasing accuracy of laboratory aids in the diagnosis of systemic lupus erythematosus there is unhappily a tendency on the part of less careful observers to affix the diagnosis of dermatomyositis to many obscure multisystemic illnesses in which weakness and fatigue are prominent, i. e., "collagen diseases" which are not demonstrably systemic lupus erythematosus or periarteritis nodosa. Such a trend is illustrated in the recent article by McCombs, Patterson, and MacMahon,[13] wherein dermatomyositis is classified as a syndrome occurring in patients with "allergic" vasculitis. In the three cases reported as dermatomyositis one is apparently a case of dermatomyositis associated with malignancy. The arthralgias, proteinuria, and pathological findings in the other two cases would not lend themselves readily to a diagnosis of dermatomyositis as generally understood. Zeek[14] noted the erroneous application of a diagnosis of periarteritis nodosa to various disorders in 1953, and Dowling[8] has recently deplored the decreasingly exact criteria for a diagnosis of dermatomyositis. Although the etiology is unknown, we feel that the documented series of dermatomyositis present enough similarity in onset, course, outcome, and pathological findings to call attention to and to protest vigorously the current trend toward broadening of the concept of dermatomyositis into a nebulous nonentity with a meaningless name.

Summary

Nineteen cases of dermatomyositis in adolescents and children seen at the University Hospital between 1935-1955 were followed to termination or to present date. The course and outcome are presented. Therapy is evaluated, and the pathological picture is reviewed.

University Hospital, University of Michigan (Dr. Curtis).

REFERENCES

1. Karelitz, S., and Welt, S. K.: Dermatomyositis, Am. J. Dis. Child. 43:1134, 1932.

2. Stuckey, E. S.: Dermato-Myositis: A Summary of the Literature and Report of Case with Commentary, Brit. J. Dermat. 47:85, 1935.

3. Keller, R.: Zur Dermatomyositis im Kindesalter, Ztschr. Kinderh. 58:551, 1936.

4. Schuermann, H.: Zur Klinik und Pathogenese der Dermatomyositis (Polymyositis), Arch. Dermat. u. Syph. 178:414, 1939.

5. Selander, P.: Dermatomyositis in Early Childhood, Acta med. scandinav., Supp. 246, p. 187, 1950.

6. O'Leary, P. A., and Waisman, M.: Dermatomyositis: A Study of 40 Cases, Arch. Dermat. & Syph. 41:1001, 1940.

7. Sheard, C., Jr.: Dermatomyositis, A. M. A. Arch. Int. Med. 88:640, 1951.

8. Dowling, G. B.: Scleroderma and Dermatomyositis, Brit. J. Dermat. 67:275, 1955.

9. Wedgwood, R. J. P.; Cook, C. D., and Cohen, J.: Dermatomyositis: Report of 26 Cases

in Children with Discussion of Endocrine Therapy in 13, Pediatrics 12:447, 1953.

10. Bezecny, R.: Dermatomyositis, Arch. Dermat. u. Syph. 171:242, 1935.

11. Curtis, A. C.; Blaylock, H. C., and Harrell, E. R., Jr.: Malignant Lesions Associated with Dermatomyositis, J. A. M. A. 150:844, 1952.

12. Wheeler, C. E.; Curtis, A. C.; Cawley, E. P.; Grekin, R. H., and Zheutlin, B.: Soft Tissue Calcification, with Special Reference to Its Occurrence in the "Collagen Diseases," Ann. Int. Med. 36:1050, 1952.

13. McCombs, R. P.; Patterson, J. F., and MacMahon, H. E.: Syndromes Associated with "Allergic" Vasculitis, New England J. Med. 255:251, 1956.

14. Zeek, P. M.: Medical Progress: Periarteritis Nodosa and Other Forms of Necrotizing Angiitis, New England J. Med. 248:764, 1953.

15. Christianson, H. B.; Brunsting, L. A., and Perry, H. O.: Dermatomyositis, Arch. Dermat. & Syph. 74:581:56.

Essential Fatty Acids and Atherosclerosis

A Critique of the Present Knowledge

GEORGE V. MANN, Sc.D., M.D., Wellesley Hills, Mass.

Recent publications from the University of Capetown, South Africa, by Bronte-Stewart and his colleagues [1,2] have led to wide interest and discussion among nutritionists and chemists concerned with atherogenesis because a new lead to the problem seems to have been created. The work of the South African group has appeared to many as a *de novo* stroke of brilliant insight and experimentation which promises to redirect further research in atherosclerosis. Furthermore, the urgency of the clinical problems which result from atherosclerosis has lead with startling rapidity to the dissemination among clinicians of "practical methods" for influencing the atherosclerotic process.[3] It is worth reviewing the history of these developments in order to find the origin of the concepts and a fair estimate of the meaning of the data and, finally, to evaluate the justification for submitting patients to regimens based on this evidence.

The fundamental working hypothesis for much of the current research in atherosclerosis relates three quantities in the following schematic plan *:

(*a*) diet ⟶ (*b*) lipidemia ⟶ (*c*) atherosclerosis

There are many logical and experimental ramifications of this formulation, which will not be considered here. For the present discussion the pertinent consideration is the relation of (*a*) to (*b*) and particularly the hypothesis which relates the kind and quantity of dietary fat in the development of lipidemia. An emphasis upon the importance of the kind of dietary fat is recent, for most nutritionists have not been convinced that the available evidence would support the argument that different fats possess differing physiological effects on serum lipid levels. This belief has been abetted by the claims of Keys [4] that the total quantity of dietary fat was the important variable.

The publication from Capetown [1]—coupled with a speculative discussion [5]—has raised the proposal that lipidemia, and by presumption atherosclerosis, is caused by a relative deficiency of a group of substances called essential fatty acids (EFA). Because of physiological relationships, pyridoxine—vitamin B_6—is also involved in this hypothesis and also, to an uncertain extent, vitamin E.

The existence of fatty acids which are essential in the mammalian diet was first proposed in 1928, by Herbert M. Evans and George O. Burr, at the University of California.[6] In the following 15 years, the chemical nature and physiological importance of the EFA were worked out, especially by Burr, who had moved to the University of Minnesota. The essentiality of these materials to other species than the rat has not been extensively studied. Observations with pigs,[7] and chickens [8] indicated that very low-fat diets lead to diminished vigor, as evidenced by poor

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* Lipidemia refers to abnormal increase of the blood lipids, as contrasted with lipemia, which refers to lactescent serum.

growth, and that the linoleic acid (or degree of fatty acid unsaturation) in the depot fats of the animals was diminished. Hansen and others have claimed cure of eczema in dogs with EFA, and Hansen, Sinclair, and Wiese have produced a scaling dermatitis in puppies kept on a low-fat diet.[9]

In studies with human beings, von Gröer [10] observed eczema in one of two infants kept on an extremely low-fat diet. Holt et al.[11] studied three infants with a low-fat diet and observed a decrease in the iodine number (a chemical measure of the degree of unsaturation of fatty acids) of the infants' serum lipids. Brown et al.[12] studied an obese man on a very low-fat diet which had produced signs of fat deficiency when fed to young rats. The only detectable change in the subject after six months was a 50% diminution of the arachidonic and linoleic acid content of the serum lipids. Hansen [13] has studied the iodine number of the serum lipids in humans with eczema. This digression was based upon the gross similarity of human "eczema" and the scaling dermatitis observed in EFA-deficient rats. He found the iodine number was reduced about 25% in eczematous infants and about 50% in eczematous adults. When such patients were treated with dietary lard or corn oil the skin improved. These findings have not been confirmed by other dermatologists.[14,15] All these early studies have been reviewed by Burr.[16]

Subsequent work, done largely with rats, revealed that six fatty acids were active as EFA, and these were at least partially interchangeable. Three of these, linoleic, linolenic, and arachidonic, were, by reason of their distributions in foodstuffs, the most available and important. Arachidonic acid seemed somewhat more potent than the others in the rat. The minimal effective dose of these materials seemed to be in the order of 80 mg. per kilogram of body weight per day when growth or cure of the typical dermatitis of deficiency in the rat were used as criteria. A significant obstacle to the transposition to human affairs of these observations with the rat has been the extreme difficulty of inducing EFA deficiency. Unlike most vitamin deficiencies, which can be produced in growing animals within a few days or weeks, EFA deficiency requires longer times and the most rigorous dietary conditions. How could such a deficiency develop in adult humans consuming a varied diet?

The answer to this may be involved in a phenomenom well known in nutritional experimentation which is called "nutritional imbalance." A high-fat diet increases riboflavin requirements, a high carbohydrate diet increases thiamin requirements. There is evidence that pyridoxine and EFA requirements are interrelated. Knowledge of this relationship began in 1935, when Hogan and Richardson [17] observed that the administration of wheat-germ oil would cure a dermatitis produced in rats with a diet low in pyridoxine. The matter was investigated by others,[18-20] and it was shown that adding fat to pyridoxine-deficient diets of rats would prevent the development of the characteristic dermatitis. Further, it was shown by Salmon [19] that pyridoxine and EFA supplement each other in the cure of "rat acrodynia," the name given the characteristic skin disorder observed in pyridoxine-deficient rats. The curative action of fats was proportional to their EFA content. Rancidity—which is partially due to unsaturated fatty acid changes in fats—led to loss of this curative potency. It is important to note that EFA would not replace pyridoxine in the rat experiments but would only prevent or cure the cutaneous lesions. The rats would die of the other manifestations of pyridoxine deficiency, which are notably renal lesions and cachexia. One worker has failed to observe this sparing action of EFA on pyridoxine deficiency.[21] The effect has been so widely demonstrated, however, that we accept the interrelationship as fact.

Schroeder has proposed [22] that pyridoxine deficiency may exist in human beings consuming a high-fat diet either by reason of an excessive intake of saturated fatty acids,

which he presumes would accentuate pyridoxine deficiency, or by an excessive intake of certain heavy metals, which might impair unspecified enzymes and by this lead to pyridoxine deficiency. There is no evidence to support Schroeder's crucial assumption that excessive saturated fatty acid intake increases the pyridoxine requirement or aggravates the deficiency syndrome. I studied this in 1941 with synthetic triglycerides.[23] Several workers have observed that the addition of saturated fatty acids to a diet low in EFA aggravates the deficiency in rats.[24-26] This may be interpreted to mean that the EFA requirement is increased by large amounts of saturated fatty acids—a nutritional imbalance. This work in rats is of crucial importance to the present problem, for both Bronte-Stewart and Sinclair have emphasized that they believe it is not a simple deficiency of EFA in the human diet which leads to the disturbance of lipid metabolism, but rather it is a disproportion in the intake of saturated and unsaturated fatty acid.

The chemical mechanism of the relationship between pyridoxine and EFA metabolism is not understood. It has been proposed that arachidonic acid can be formed in the body from linoleic acid in the presence of pyridoxine, but the evidence for this is indirect, and other conclusions are equally valid.[27] Neither has it been shown that arachidonic behaves differently than linoleic acid vis-a-vis lipid metabolism. Sinclair argues [5] that EFA deficiency obstructs cholesterol metabolism and leads to lipidemia by reason of excessive esterification of cholesterol with saturated fatty acids, the unsaturated being unavailable. These cholesterol esters, he supposes, are not readily disposed of. It has been shown that EFA deficiency leads to an accumulation of cholesteryl esters in the liver [28] and in the skin.[29] Bromer and Day [30] also observed that cholesterol feeding accelerated the appearance of EFA deficiency in young rats and delayed the response to methyl linoleate treatment. Recently it has been shown that cholesterol feeding hastens the onset and aggravates the intensity of EFA deficiency in rats made diabetic with alloxan.[31]

The complications of this problem are indicated by the work of Kritchevsky et al.,[32] who have confirmed the original observation of Swell et al.[33] that rats fed cholesterol along with unsaturated fats developed higher serum cholesterol levels than when saturated fats were fed. Kritchevsky used rabbits fed cholesterol in one of three lipid vehicles with varying degrees of saturation and observed the highest serum cholesterol levels but the least amount of atherosclerosis in rabbits fed the most unsaturated fats. Obviously these findings are not readily fitted with the recent human data that will be discussed.

Sinclair's discussion [5] deserves close consideration because it has caused much of the present furor over EFA and atherosclerosis. While it is conceptually a brilliant piece, it suffers from the inclusion of errors of fact or of uncertainties which are often of crucial importance to the argument. Reference has been made to the premature acceptance of the belief that pyridoxine functions in the conversion of linoleic to arachidonic acid —at best an uncertain hypothesis. Sinclair emphasizes that the requirement of the male animal for EFA is at least five times that of females. This is an oversimplification, because the biological assays of EFA requirements are not strictly quantitative in male rats and in female rats the assay is obscured by toxicity of EFA at levels very near those which give optimum growth.[34] Sinclair states that Kinsell et al.[35] and Bronte-Stewart et al.[1] have shown that linoleic acid lowers serum cholesterol in man. This has not been shown to be the effective substance in their experiments, although this remains an attractive hypothesis. Sinclair cites the production of "atherosclerosis" in monkeys kept on pyridoxine-deficient diets as proof of the relation of pyridoxine to atherogenesis. The changes produced in monkeys were not atherosclerosis, but rather an intimal fibrosis, free of lipid and largely in peripheral, muscular arteries.[36] He ob-

serves in passing that in his laboratory pyridoxine-deficient rats are given large amounts of EFA, and so vascular disease had not been seen. Other workers find that EFA will prevent pyridoxine deficiency or at least greatly delay its onset.

Sinclair then poses four possible mechanisms which may lead to human atherosclerosis: (1) diets very low in EFA; (2) diets fairly low in EFA, high in cholesterol; (3) diets fairly low in EFA, high in saturated fatty acids; (4) diets fairly low in EFA and low in pyridoxine. The most plausible combination would seem to be mechanisms (2) and (3).

There is no specific or accurate information about EFA intake in man, nor—because of the instability and distribution of these fatty acids—is such information likely to be obtained. When it is recalled that corn oil (Mazola) and cottonseed oil (Wesson Oil), as well as many other seed oils, peanut and olive, e. g., are widely used as human foods and that these oils are rich in EFA (corn oil contains 55% linoleic acid, cottonseed oil, 50%) it is difficult to see how the dietary intake of EFA by Americans can be low in these materials. Using rat data as a guide, we presume that 10-20 gm. per day of EFA may be optimal for human beings. Nyrop [37] has discussed the matter of the optimal EFA intake with the limited available data. He concludes that about 15 gm. of EFA per 2500 Cal. is adequate to prevent lipidemia. He also observes that the EFA content of the diet in the United Kingdom steadily diminished from 5 gm. per capita per day in 1939 to 2 gm. in 1952, and the content of arachidonic acid diminished from 0.8 gm. to 0.3 gm. in the same period. Human milk contains about 13.3 gm. of EFA per 2500 Cal., which may be a confirmation of Nyrop's estimate from experimental data. Greenberg et al.[34] have developed a biological assay for EFA, using depleted rats. With this test applied to commercial fats, they obtained the results shown in Table 1.

TABLE 1.—*Essential Fatty Acid Content of Commercial Fats*

Commercial Samples	Essential Fatty Acid Content, Gm./100 Gm.		
	Linoleic	Linolenic	Arachidonic
Butter I	3.2	0.9	0.2
Butter II	4.0	1.2	0.2
Cottonseed oil hydrogenated (selective)*	2.2	0	0
Cottonseed oil hydrogenated (nonselective)	7.1	0	0
Margarine I	5.0	0	0
Margarine II	5.8	0	0
Margarine III	4.6	0	0
Margarine IV containing 1.5% added cottonseed oil	5.1	0	0
Cottonseed oil	51.9	0	0
Coconut oil (hydrogenated)	0	0	0

* Hydrogenation is directed toward the tetraenoic acids especially.

The catalytic hydrogenation of natural fats proceeds from the most highly unsaturated fatty acids to the less saturated.[38] Since the end-point in the industrial process is determined by organoleptic criteria, it follows that the necessary degree of "hardness" of the fat—as well as the improved resistance to oxidation on storage—will result only after practically all the arachidonic and linolenic acids and most of the linoleic are gone.

It follows from these data that the ancient butter versus oleomargarine controversy is involved in the present issue. Orr [39] stated that in 1936 the per capita consumption in the United Kingdom of margarine was 3.7 kg. annually and of butter, 11.5 kg. In 1954, Nyrop [40] found the corresponding figures to be 9.5 kg. of margarine and 7.2 kg. of butter. The U. S. Agriculture Department publishes data on the consumption of food in the United States. These are the so-called "disappearance data" derived by subtracting the amount of existing food supplies from food produced and dividing the difference by the population count. These data are the kind which are so frequently misused by entrepeneurs seeking to prove some association between diet and heart disease. Table 32 in Agriculture Handbook 62 [41] does indicate in relative terms the profound changes of butter and margarine "disappearance" in the interval of 1909-1952. The "other edible oils," comprising salad oils which are native vegetable oils rich in EFA, also deserve

TABLE 2.—*Annual per Capita Consumption in Pounds as Measured by Retail Weight of Food Disappearing*

Year	Butter	Margarine	"Other Edible Oils"
1909	17.5	1.2	1.5
1930	17.3	2.6	5.9
1940	16.7	2.4	7.3
1952	8.7	7.8	8.8

attention. The increase in "consumption" of these vegetable oils has paralleled the increase of margarine (Table 2).

This discussion has been concerned largely with the data of laboratory experimentation of sufficient age that they have been subjected to critical evaluation. Consider now more recent events and particularly the results of clinical investigation, which, by reason of their meager quantity, imperfections of experimental design, or variability of response are much more difficult to evaluate. Such data illustrate the interpretive problems which face almost every active medical researcher. Such interpretation is a highly subjective and a "sometime thing."

Davidson[42] has reviewed the complex problem of the effects of low-fat diets, low-cholesterol diets, and the effects of the so-called lipotropic agents—choline, methionine, and inositol. Two facts seemed to appear. Drastic reduction of the dietary fat, i. e., to 50 gm. per day or less, would usually produce a reduction of the serum cholesterol. The usual levels of dietary cholesterol (up to 1000 mg. per day) seemed to have little immediate effect upon the serum cholesterol levels. This fact has the important qualification that it arises from short-term studies, and exposure for years or decades may make this factor more important than it now seems.[43] The numerous indecisive reports of a serum cholesterol reducing effect of various "phospholipids," choline, etc.,[44-47] may, in retrospect, have been based upon some physiological effect of the fatty acids in these chemicals rather than upon the intact compounds, but this is speculative.

Finally, there are the studies of the effects of various kinds of dietary fat on the serum lipid levels of human subjects. Perhaps the most impressive single piece of this research is the publication in 1952, of Groen and his colleagues, from Amsterdam.[48] These workers studied 60 normal adult subjects during three periods of 12 weeks each. They found that a vegetable diet generally lowered the serum cholesterol levels, a high-meat diet typical of the United States generally raised the serum cholesterol levels, and a low-meat diet typical of Holland had an intermediate effect. Since the fat and calory contents of the diets were similar, and since dietary cholesterol per se can scarcely have contributed to these results, it follows that the authors must have observed the effect of vegetable fat. Since some of the fat in the vegetable diet (V) and Dutch diet (L) was margarine, the effects may have been diminished by this circumstance. Nevertheless, this was and is a classical study with respect to conception, design, and execution. More such studies would resolve much of the present confusion. The authors did not reach the conclusion that the observations were due to dietary fat differences, although they included that possibility along with calories and animal protein. They did, in the discussion, project the experiment which would have answered this decisively. A sentence is worth quoting: "It further followed from this investigation that an exclusively vegetable diet reduces the blood cholesterol even if the fat content of the diet is rather high, viz., varying between 90 and 125 gm. per day. . . ."

There is also the series of publications of Kinsell and his colleagues at Oakland, Calif.[49] Kinsell found that subjects fed very high-vegetable-fat diets by means of a liquid formula administered through a tube displayed a reduction of the serum cholesterol level. There were two difficulties with these experiments. They were hampered by the existence of multiple experimental variables, e. g., the subjects were often ill with endocrine disorders, the dietary treatment was mingled with hormonal treatment, and the initial cholesterol levels of the subjects were often bizarre, i. e., very low or very high. The last criticism is also applicable to

Bronte-Stewart's experiment with six men, four of whom were recovering from vitamin-deficiency states and several of whom had initially very low cholesterol levels, presumably a consequence of physiological stress.[50]

Beveridge and his colleagues, in Canada, have published a series of papers[51,52] which show more conclusively than did Bronte-Stewart that both the kind and quantity of dietary fat influence lipidemia. Groups of 36 to 49 young men were fed high-vegetable-fat diets which lowered the blood cholesterol; animal fats in the diet then raised the cholesterol. Very low-fat diets lowered the cholesterol. Their conclusion was as follows: ". . . in animal fat a factor or factors act to elevate plasma cholesterol levels and a factor or factors act in corn oil to depress plasma cholesterol levels." These were short experiments, generally eight days in duration.

Malmros and Wigand[53] have described reductions of the serum cholesterol levels in both hyper- and normocholesteremic persons by dietary means. The effect was greatest in the first week of treatment but continued slowly thereafter. A sentence from their conclusions is as follows: "The favorable results obtained with corn oil might possibly be due to the abundance of essential fatty acids in this kind of fat." This statement may establish their priority for this concept.

Ahrens and his colleagues, in New York City,[54,55] fed seven patients measured diets under research conditions and found that diets containing corn oil produced the greatest reductions of serum cholesterol. Fat was fed at a level of 40% of the total calories. Addition of cholesterol to the corn-oil diet until as much as 4000 mg. per day was added had no effect. This work was carefully done, and the conclusions were definite. They are limited only by the small number of subjects. The authors reached the following conclusions: "The reductions of liped levels following the feeding of plant fats is dependent upon the specific fat fed, is not due to the decreased intake of cholesterol per se, and may be more pronounced with a high intake of fat."

All these experiments lead then to Bronte-Stewart's recent work and to the hypothesis proposed by Sinclair. It is apparent that widespread interest will lead to intensive clinical trials of vegetable oils. The evaluation of this dietary effect needs only the passage of time. Other, more technical, requirements for the understanding of the mechanism of these phenomena will need more specialized work. An immediate and economically profound problem is that which confronts the food industry and margarine manufacturers. One immediate proposal may be for the addition to margarine of some untreated oil rich in EFA (Table 1). How much should be added? This must await determination of EFA requirements, and since EFA deficiency is probably an imbalance, requirements will depend upon a better understanding of the balancing factors. Three of these are (1) the intake of saturated fatty acids, (2) the possible role of pyridoxine, and (3) the role of vitamin E, which is presently believed to act as a preserver or protector of the highly unstable EFA in food stuffs and in the intestinal tract. Finally, it should be reemphasized that all this is concerned with the relation of diet to lipidemia, factors (*a*) and (*b*) in the following formulation:

$$\underset{\text{diet}}{(a)} \longrightarrow \underset{\text{lipidemia}}{(b)} \longrightarrow \underset{\text{atherosclerosis}}{(c)}$$

What then is the relation of (*b*) to (*c*)? And what is the relation of (*c*) to clinical events such as coronary heart disease and cerebrovascular disease, which are the ultimate problems? It is worthwhile to read the comment of Morris[56] on this problem. He observes that we obscure this problem by equating atherosclerosis and coronary thrombosis. The latter may be a poor index of the former.

200 Oakland St.

REFERENCES

1. Coronary-Artery Disease, Letters to the Editor, Lancet 1:101, 1956.

2. Bronte-Stewart, B.; Antonis, A.; Eales, L., and Brock, J. F.: Effects of Feeding Different Fats on Serum-Cholesterol Level, Lancet 1:521-526, 1956.

3. Schroeder, H. A.: A Practical Method for the Reduction of Plasma Cholesterol in Man, J. Chron. Dis. 4:461-468, 1956.

4. Keys, A., and Anderson, J. T.: The Relationship of the Diet to the Development of Atherosclerosis in Man, in Symposium on Atherosclerosis, Publication 338, National Research Council, 1954, pp. 181-197.

5. Deficiency of Essential Fatty Acids and Atherosclerosis, Etcetera, Letters to the Editor, Lancet 1:381-383, 1956.

6. Evans, H. M., and Burr, G. O.: A New Dietary Deficiency with Highly Purified Diets: III. The Beneficial Effect of Fat in the Diet, Proc. Soc. Exper. Biol. & Med. 25:390-397, 1928.

7. Ellis, N. R., and Zeller, J. H.: Soft Pork Studies: IV. The Influence of a Ration Low in Fat upon the Composition of the Body Fat of Hogs, J. Biol. Chem. 89:185-197, 1930.

8. Russell, W. C.; Taylor, M. W., and Polskin, L. J.: Fat Requirements of the Growing Chick, J. Nutrition 19:555-562, 1940.

9. Hansen, A. E.; Sinclair, J. G., and Wiese, H. F.: Sequence of Histologic Changes in Skin of Dogs in Relation to Dietary Fat, J. Nutrition 52:541-554, 1954.

10. von Gröer, F.: Zur Frage der praktischen Bedeutung des Nähwertbegriffes nebst einigen Bermerkungen über das Fettminimum des menschlichen Säuglings, Biochem. Ztschr. 97:311-329, 1919.

11. Holt, L. E.; Tidwell, H. C.; Kirk, C. M.; Cross, D. M., and Neale, S.: Studies in Fat Metabolism: I. Fat Absorption in Normal Infants, J. Pediat. 6:427-489, 1935.

12. Brown, W. R.; Hansen, A. E.; Burr, G. O., and McQuarrie, I.: Effects of Prolonged Use of Extremely Low-Fat Diet on an Adult Human Subject, J. Nutrition 16:511-524, 1938.

13. Hansen, A. E.: Serum Lipids in Eczema and in Other Pathologic Conditions, Am. J. Dis. Child. 53:933-946, 1937.

14. Ginsberg, J. E.; Bernstein, C., Jr., and Iob, L. V.: Effect of Oils Containing Unsaturated Fatty Acids on Patients with Dermatitis, with a Brief Report on an Experimental Study in Guinea-Pigs, Arch. Dermat. & Syph. 36:1033-1038, 1937.

15. Taub, S. J., and Zakon, S. J.: The Use of Unsaturated Fatty Acids in the Treatment of Eczema (Atopic Dermatitis, Neurodermatitis), J. A. M. A. 105:1675, 1935.

16. Burr, G. O.: Significance of the Essential Fatty Acids, Fed. Proc. 1:224-233, 1942.

17. Hogan, A. G., and Richardson, L. R.: Plural Nature of Vitamin B, Nature, 136:186, 1935.

18. Birch, T. W.; György, P.: XLVII. A Study of the Chemical Nature of Vitamin B_6 and Methods for Its Preparation in a Concentrated State, Biochem. J. 30:304-315, 1936.

19. Salmon, W. D.: The Effects of Certain Oils in Alleviating Localized Erythematous Dermatitis (Acrodynia or Vitamin B_6 Deficiency) in Rats, J. Biol. Chem. 123:XXXII, 1938.

20. Schneider, H. A.; Ascham, J. K.; Platz, B. R., and Steenbock, H.: The Anti-Acrodynic Properties of Certain Foods, J. Nutrition 18:99-104, 1938.

21. Emerson, G. A.: Absence of Supplementary Relationships in Requirements for Pyridoxin and Essential Fatty Acids, Proc. Soc. Exper. Biol. & Med. 47:445-448, 1941.

22. Schroeder, H. A.: Is Atherosclerosis a Conditioned Pyridoxal Deficiency? J. Chron. Dis. 2:28-41, 1955.

23. Mann, G. V.: The Relation of Pyridoxine to Fat Metabolism, Dissertation, The Johns Hopkins University, 1942.

24. Evans, H. M., and Lepkovsky, S.: Vital Need of the Body for Certain Unsaturated Fatty Acids: II. Experiments with High Fat Diets in Which Saturated Fatty Acids Furnish the Sole Source of Energy, J. Biol. Chem. 96:157-164, 1932.

25. Sinclair, R. G.: Evidence of the Synthesis of Essential Unsaturated Fatty Acids by the Rat, J. Biol. Chem. 114:XCIV, 1936.

26. Deuel, H. J., Jr.; Greenberg, S. M.; Anisfeld, L., and Melnick, D.: The Effect of Fat Level of the Diet on General Nutrition: VIII. The Essential Fatty Acid Content of Margarines, Shortenings, Butters, and Cottonseed Oil as Determined by a New Biological Assay Method, J. Nutrition 45:535-549, 1951.

27. Witten, P. W., and Holman, R. T.: Polyethenoid Fatty Acid Metabolism: VI. Effect of Pyridoxine on Essential Fatty Acid Conversions, Arch. Biochem. 41:266-273, 1952.

28. Alfin-Slater, R. B.; Aftergood, L.; Wells, A. F., and Deuel, H. J., Jr.: The Effect of Essential Fatty Acid Deficiency on the Distribution of Endogeneous Cholesterol in the Plasma and Liver of the Rat, Arch. Biochem. 52:180-185, 1954.

29. Basnayake, V., and Sinclair, H. M., in Proceedings of the Second International Conference on Lipids, Ghent, 1955.

30. Bromer, W. W., and Day, H. G.: News Report, Chem. Engin. News 31:3964, 1953.

31. Essential Fatty Acids, Diabetes, and Cholesterol, Letters to the Editors, Arch. Biochem. 57: 520-521, 1955.

32. Kritchevsky, D.; Moyer, A. W.; Tesar, W. C.; McCandless, R. F. J.; Logan, J. B.; Brown, R. A., and Englert, M. E.: Cholesterol

Vehicle in Experimental Atherosclerosis: II. Influence of Unsaturation, Am. J. Physiol. 185:279-280, 1956.

33. Swell, L.; Flick, D. F.; Field, H., Jr., and Treadwell, C. R.: Role of Fat and Fatty Acid in Absorption of Dietary Cholesterol, Am. J. Physiol. 180:124-128, 1955.

34. Greenberg, S. M.; Calbert, C. E.; Savage, E. E., and Deuel, H. J., Jr.: The Effect of Fat Level of the Diet on General Nutrition: VI. The Interrelation of Linoleate and Linolenate in Supplying the Essential Fatty Acid Requirement in the Rat, J. Nutrition 41:473-486, 1950.

35. Kinsell, L. W., and Michaels, G. D.: Hormonal-Nutritional-Lipid Relationship, Fed. Proc. 14:661-666, 1955.

36. Rinehart, J. F., and Greenberg, L. D.: Arteriosclerotic Lesions in Pyridoxine-Deficient Monkeys, Am. J. Path. 25:481-491, 1949.

37. Fats and Disease, Letters to the Editor, Lancet 1:914-915, 1956.

38. Deuel, H. J., Jr.: The Lipids: Their Chemistry and Biochemistry, New York, Interscience Publishers, Inc., 1951, Vol. 1, p. 148.

39. Orr, J. B.: Food, Health and Income: National Survey of Nutrition, Lancet 1:679-681, 1936.

40. Hardened Fats and Lung Cancer, Letters to the Editor, Lancet 2:1288, 1954.

41. Consumption of Food in the United States 1909-52, Agriculture Handbook 62, Agriculture Department, September, 1953.

42. Davidson, J. D.: Diet and Lipotropic Agents in Arteriosclerosis, Am. J. Med. 11:736-748, 1951.

43. Mann, G. V., and Andrus, S. B.: Xanthomatosis and Atherosclerosis Produced by Diet in an Adult Rhesus Monkey, J. Lab. & Clin. Med. 48:533-550, 1956.

44. Pottenger, F. M., Jr., and Krohn, B.: Reduction of Hypercholesterolemia by High-Fat Diet Plus Soybean Phospholipids, Am. J. Digest. Dis. 19:107-109, 1952.

45. Steiner, A.: Action of Choline on Experimental Aortic Atherosclerosis, Proc. Soc. Exper. Biol. & Med. 39:411-413, 1938.

46. Kesten, H. D., and Silbowitz, R.: Experimental Atherosclerosis and Soya Lecithin, Proc. Soc. Exper. Biol. & Med. 49:71-73, 1942.

47. Steiner, A., and Domanski, B.: Effect of Feeding of "Soya Lecithin" on Serum Cholesterol Level of Man, Proc. Soc. Exper. Biol. & Med. 55:236-238, 1944.

48. Groen, J.; Tjiong, B. K.; Kamminga, C. E., and Willebrands, A. F.: The Influence of Nutrition, Individuality and Some Other Factors, Including Various Forms of Stress, on the Serum Cholesterol: An Experiment of 9 Months' Duration in 60 Normal Volunteers, Voeding 13:556-587, 1952.

49. Fats and Disease, Letters to the Editor, Lancet 1:1017-1019, 1956.

50. Mann, G. V., and White, H. S.: The Influence of Stress on Plasma Cholesterol Levels, Metabolism 2:47-58, 1953.

51. Mayer, G. A.; Connell, W. F.; DeWolfe, M. S., and Beveridge, J. M. R.: Diet and Plasma Cholesterol Levels, Am. J. Clin. Nutrition 2:316-322, 1954.

52. Beveridge, J. M. R.; Connell, W. F., and Mayer, G.: Further Studies on Dietary Factors Affecting Plasma Lipid Levels in Humans, Circulation 12:499, 1955.

53. Malmros, H., and Wigand, G.: Treatment of Hypercholesteremia, Minnesota Med. 38:864-870, 1955.

54. Ahrens, E. H., Jr.; Blankenhorn, D. H., and Tsaltas, T. T.: Effect on Human Serum Lipids of Substituting Plant for Animal Fat in Diet, Proc. Soc. Exper. Biol. & Med. 86:872-878, 1954.

55. Ahrens, E. H., Jr.; Tsaltas, T. T.; Hirsch, J., and Insull, W., Jr.: Effects of Dietary Fats on the Serum Lipides of Human Subjects, J. Clin. Invest. 34:918, 1955.

56. Fats and Disease, Letters to the Editor, Lancet 1:687-689, 1956.

Demecolcine (Colcemid) Toxicity

CAPT. THOMAS W. SHEEHY (MC) and CAPT. JAMES W. RANSONE (MC), U. S. Army

In 1950, demecolcine (Colcemid) was isolated from Colchicum autumnale.[1] In 1953, Moeschlin et al.[2] reported its use and beneficial effects in a case of chronic granulocytic leukemia, with a fall in white cell count, a decrease in splenomegaly, and increased erythroid elements in the marrow. The doses ranged from 3 to 8 mg. daily.

In 1955, Leonard and Wilkinson[3] confirmed Moeschlin's findings in eight cases of chronic granulocytic leukemia in which a dosage of 3 to 10 mg. daily for four to nine months was used. The toxic effects were mild and consisted of some loss of scalp hair, erythema of the scrotum, and, in one case, congestion and erythema of the pharynx.

Our report is prompted by the sudden and severe side-effects in one patient with follicular lymphoma and in another patient with chronic granulocytic leukemia who were both given demecolcine.

Report of Cases

CASE 1.—A 38-year-old white man was admitted on May 15, 1956, because of chills, fever, night sweats, and a 10 lb. weight loss due to malignant follicular lymphoma. Diagnosis had been established one year earlier following an inguinal node biopsy. Originally, the patient manifested axillary, inguinal, and supraclavicular lymphadenopathy which responded well to radiation therapy.

In September, 1955, weakness and fatigue developed, and a subsequent study revealed pancytopenia due to hypersplenism. Splenectomy was successful in alleviating this complication. Postoperatively, the blood elements returned to normal. Pathological study of the spleen was consistent with the original diagnosis. A liver biopsy showed lymphocytic infiltration.

Three months prior to the patient's present admission, constitutional symptoms developed for the second time. These became progressively worse, and he was readmitted for study and therapy.

His past history was negative except for pneumonia in 1945, with subsequent penicillin reaction manifested by a maculopapular eruption and urticaria.

Physical examination revealed a mesomorphic white man in no acute distress. His weight was 165 lb., his temperature, 100.2 F orally. His blood pressure was 124/82; his pulse, 74, and his respirations, 20. He was oriented and showed no overt signs of marked weight loss. A 3 by 5 cm. mass was present in the left supraclavicular area, and shot-like nontender nodes were found in both axillary and inguinal regions. Hepatomegaly of moderate degree—the liver extending 2.5 cm. below the right costal margin—was the only other positive finding.

The initial laboratory data showed a white blood cell count of 8600, with 72% neutrophils, 22% lymphocytes, 2% monocytes, 1% basophils, 3% eosinophils, hemoglobin 15.2 gm., hematocrit 44%, and platelets 294,000 by phase microscopy (Fig. 1). The serology was negative. The blood urea nitrogen and liver-function studies were normal. Roentgenographic examinations of the chest and upper and lower gastrointestinal tracts were also normal.

The patient was treated with a total of 30 mg. of mechlorethamine hydrochloride (nitrogen mustard) from May 17 to May 20, 1956, and x-ray therapy totaling 4500 r to the axillary and inguinal regions was given over the following month. He improved and went on leave. After his return in July, 1956, however, he had a recurrence of symptoms accompanied by loss of appetite and weight but without significant lymphadenopathy. A subsequent trial of prednisone was unsuccessful in alleviating his symptoms, and he remained febrile, with his daily temperature ranging between 100 and 102 F orally.

On Aug. 14, 1956, demecolcine therapy was begun, 1 mg. every other day. On Aug. 23, the dosage was increased to 1 mg. daily; on Sept. 6, to 2 mg. daily, and on Sept. 11, to 3 mg. daily. The dosage was increased again on Sept. 16, to 4 mg. daily. Twenty-four hours later the patient com-

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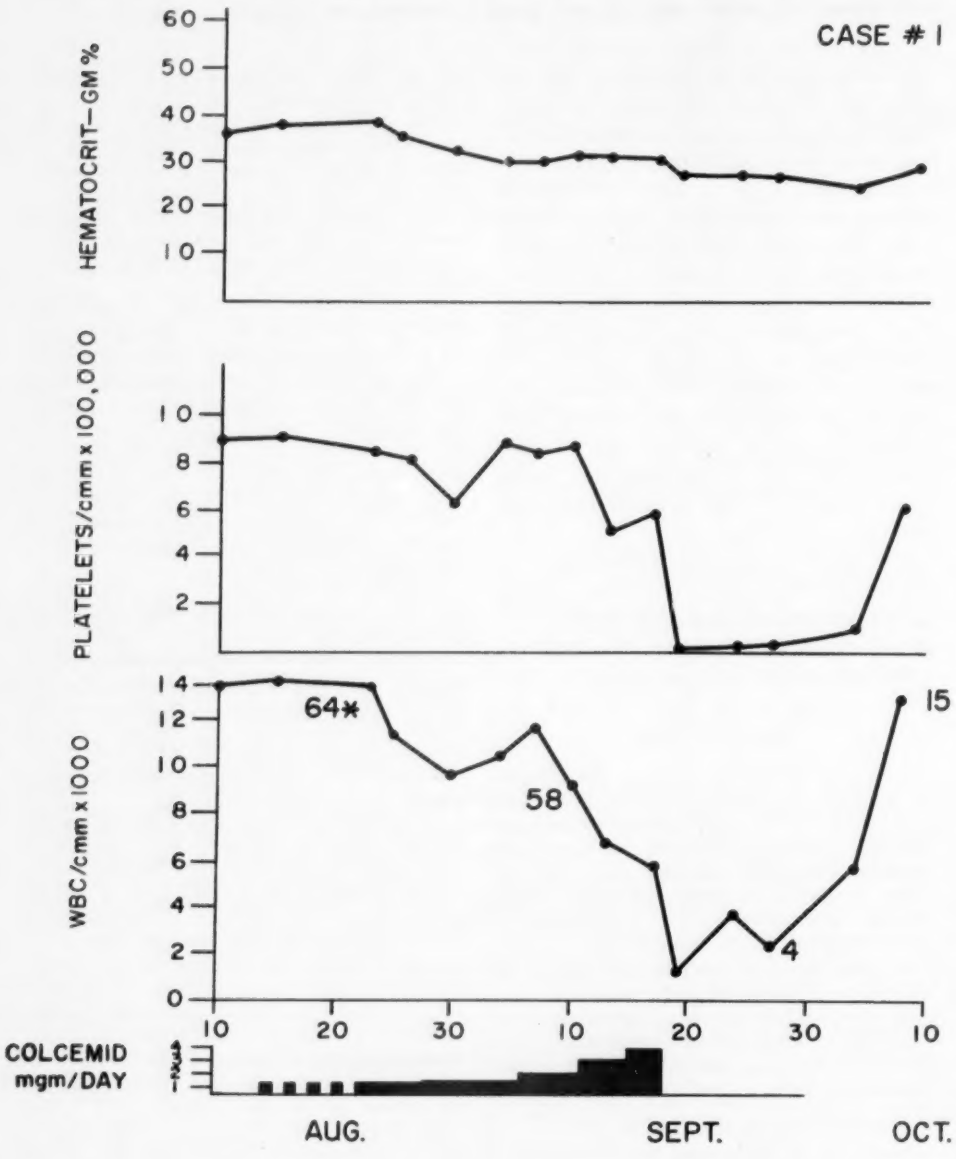
Department of Hematology, Walter Reed Army Institute of Research (Capt. Sheehy), and Department of Medicine, Walter Reed Army Hospital (Capt. Ransone), WRAMC, Washington 12, D. C.

plained of pruritus over the anterior abdomen and thighs, and on the evening of Sept. 18 a maculopapular erythematous rash developed which subsequently became confluent, covering the entire body. At this time medication was discontinued. The following day bullous-like lesions varying from 0.5 to 1.5 cm. in diameter were noted scattered over the entire trunk. Ulceration of the mucous membranes of the mouth was observed, and hyperemia and swelling of the soft palate,



* NUMBERS INDICATE PERCENT OF GRANULOCYTES

Fig. 1.—Thrombocytopenia and leukopenia in a patient with giant follicular lymphoma (lymphoblastic type) treated with demecolcine (Colcemid).

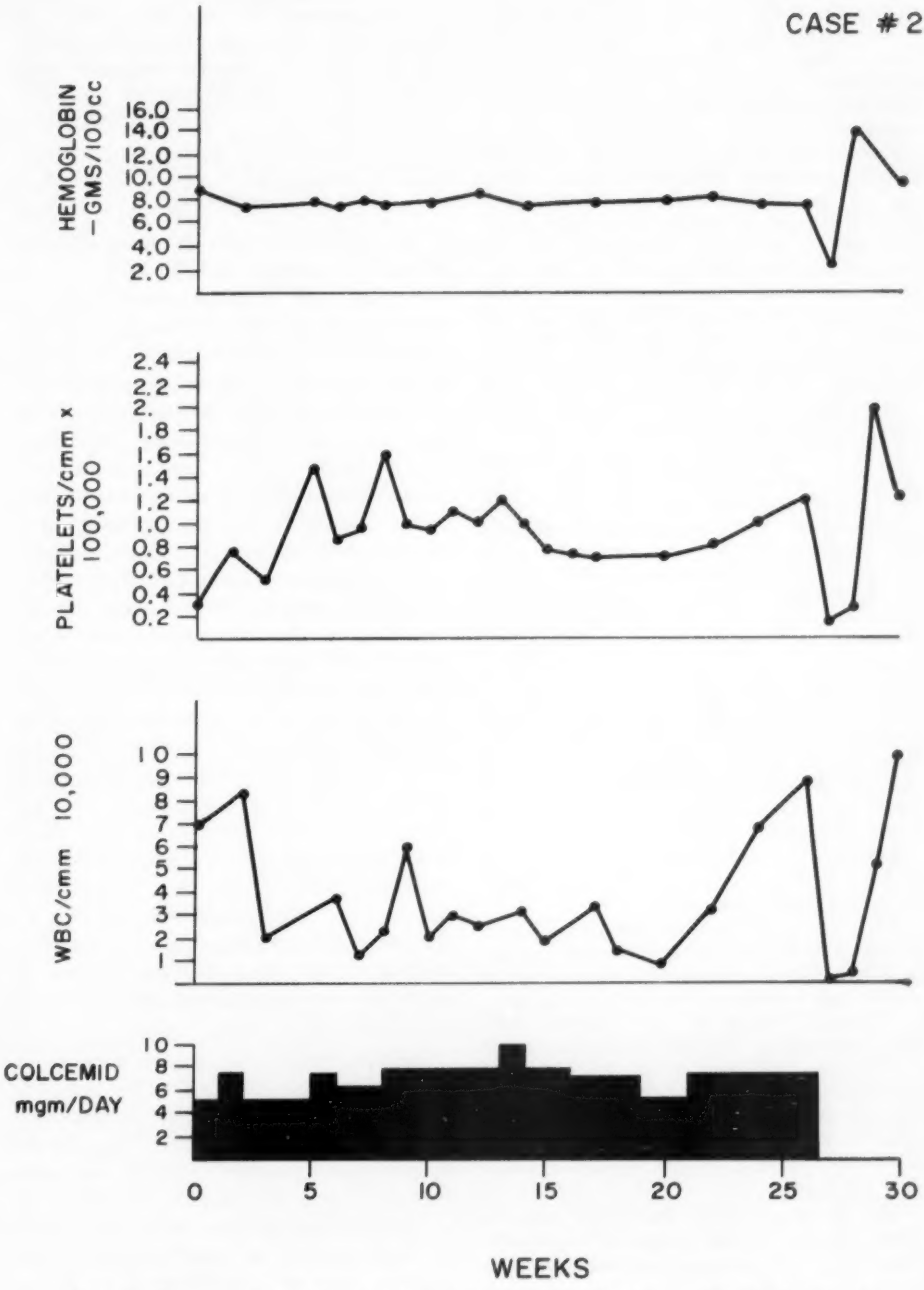


Fig. 2.—Pancytopenic reaction to demecolcine (Colcemid) after prolonged therapy in chronic granulocytic leukemia.

uvula, and pharyngeal tissues ensued, making it impossible for the patient to take food or liquids. During this time, the patient's oral temperatures varied between 102 and 106 F. Simultaneously, with the onset of the skin lesions, his pancytopenia ensued. His white cell count fell to 1450, with 2% neutrophils and 98% lymphocytes; his hematocrit, from 32% to 24%, and his platelets, from an average level of 650,000 to 14,500. Therapy throughout this period consisted of the use of prednisone, tetracycline, streptomycin, whole blood, and intravenous fluids. By Sept. 25, 1956, he was afebrile, but total alopecia developed the following week. His white blood cells began to reappear rapidly, as did his platelets, and by Oct. 5, 1956, the white blood cell count was 7500, with 8% neutrophils, 88% lymphocytes, 4% monocytes, and platelets 150,000. It was not until Oct. 18, however that his neutrophils were normal, and by then his platelets exceeded 1,000,000. Platelet and white cell agglutinin studies were negative.[4-6]

Case 2.—Diagnosis in this 71-year-old white woman was established in March, 1955, by sternal marrow aspiration as chronic granulocytic leukemia after a 12-month history of easy bruising. She was treated initially with intravenous radioactive P^{32}, but this was discontinued because of thrombocytopenia. In March, 1956, demecolcine therapy was begun. On a weekly basis, the dose varied between 5 and 10 mg. a day, depending upon her blood cell counts. The white cell counts varied between 9000 and 89,000; hemoglobin, 7 to 9 gm, and direct platelet counts, 30,000 to 165,000. Objectively and subjectively she remained in fair condition, but on Sept. 9, 1956, while on a trip, unexplained nausea occurred which was soon followed by extreme dizziness, drowsiness, blurred vision, and marked weakness. On Sept. 13, she was admitted to Walter Reed Army Hospital. She appeared acutely and severely ill, with marked pallor and mental confusion.

There was no evidence of adenopathy, hepatosplenomegaly, or petechiae upon physical examination, but fundoscopic examination revealed bilateral, diffuse, and flame-shaped retinal hemorrhages.

Laboratory data on admission showed a white blood cell count of 650, with 32% neutrophils, 5% band forms, 66% lymphocytes, 2% monocytes; hemoglobin, 2.5 gm., and hematocrit, 8.5%. No platelets were seen by phase microscopy (Fig. 2). Both the blood urea nitrogen and serum uric acid levels were normal. Sternal marrow aspiration was unsuccessful.

The patient was given transfusions and antibiotics because of her anemia and leucopenia. Seven days after admission her white cell count was 4850, with 61% neutrophils, 28% stab forms, 1% myelocytes, 2% metamyelocytes, and 39% lymphocytes; her hemoglobin after transfusion was 14.2 gm., with 27,000 platelets. Fourteen days after admission her white cell count rose to 54,000, with 46% neutrophils, 11% stab forms, 11% metamyelocytes, 3% myelocytes, 11% lymphocytes, and 18% monocytes. In spite of her extremely grave condition on admission, she improved rapidly and was soon ambulatory. There was no skin eruption or depilation at any time.

Comment

The beneficial effects of demecolcine in chronic granulocytic leukemia reported by Moeschlin has recently been verified by Leonard and Wilkinson. Both groups report demecolcine as having definite value in chronic granulocytic leukemia, with a distinct depressant action on the granulocytes, rapid reduction in splenomegaly, and definite clinical improvement. Our patient with chronic granulocytic leukemia showed such effects. Leonard felt demecolcine had a definite advantage over busulfan (Myleran) in that it did not produce thrombocytopenia or aplastic anemia. Thrombocytopenia and leucopenia developed rapidly in both of our patients after apparent tolerance of the drug over a considerable period of time. Case 1 showed arrest of the bone marrow at the myelocytic stage and a severe platelet fall from the previously high postsplenectomy platelet levels. Case 2 was positive for agglutinins to both platelets and white blood cells. Moeschlin reported granulocytopenia of fairly sudden onset in a patient with carcinoma of the gallbladder but did not encounter thrombocytopenia. The point of interest in our cases was the rapidity of onset of thrombocytopenia and granulocytopenia.

To date, toxic reactions with demecolcine are few, probably because of its relatively recent introduction. One case of maculopapular eruption occurred after 8 mg. of the drug was given orally.[7] Pruritus and scarlatiniform dermatitis were found in 2 of 27 patients treated by Bock and Gross,[8] and 5 of these patients had partial alopecia. Total alopecia after the administration of 14 mg. of demecolcine has been reported recently.[9] Severe thrombocytopenia and exfoliative

dermatitis, to our knowledge, has not been previously reported. The delayed onset of the dermatitis in Case 1 leads us to consider drug sensitivity as the basic etiology. Furthermore, the finding of positive agglutinins in Case 2 raises the question of drug sensitivity as a cause of thrombocytopenia.

Several reports (Kuzell,[10] Smyth,[11] Colsky[7]) have recently appeared in the literature emphasizing the use of demecolcine in the treatment of acute gouty arthritis. The dosage utilized was admittedly smaller than that given to our patients, but in view of its possible increasing utilization in the therapy of leukemia or gout, the complications herein reported should be considered.

Summary

Two cases of severe toxic reactions to demecolcine therapy are reported.

These occurred in one patient with giant follicular lymphoma (lymphoblastic-type) and in another with chronic granulocytic leukemia.

Lieut. Col. William H. Crosby, Department of Hematology, WRAMC, assisted in the preparation of this paper.

Department of Hematology, Walter Reed Army Institute of Research, WRAMC, Washington 12, D. C.

REFERENCES

1. Santavy, F. and Reichstein T.: Isolierung neuer Stoffe aus den Samen der Herbstzeitlose Colchicum autumnale L. Substanzen der Herbstzeitlose und ihre Derivate, Helvet. chim. acta: 33:1606, 1950.

2. Moeschlin, S.; Meyer, H., and Lichtman, A.: Ein neues Colchicum-Nebenalkaloid (Demecolcin Ciba) als Cytostaticum myeloischer Leukämen, Schweiz. med. Wchnschr. 83:990, 1953.

3. Leonard, B. J., and Wilkinson, J. F.: Desacetylmethylcolchicine in Treatment of Myeloid Leukæmia, Brit. M. J. 1:874, 1955.

4. Dausset, J.; Delafontaine, P., and Fleuroit, Y.: Agglutination et destruction "in vitro" des plaquettes normales par le sérum d'une malade atteinte de purpura thrombopénique aigu: Inhibition par ce sérum de la rétraction du caillot normal, Sang 23:373, 1952.

5. Dausset, J.: Technique de recherche d'une leuco-agglutinine, Rev. franç. etudes cliniq. biol. 1:241, 1956.

6. Dausset, J.: Personal communication to the authors.

7. Colsky, J.; Wallace, S., and Banowitch, M. M.: Desacetylmethylcolchicine in Acute Gouty Arthritis, New England J. Med. 253:730, 1955.

8. Bock, H. E., and Gross, R.: Leukämie- und Tumorbehandlung mit einem Nebenalkaloid aus Colchicum autumnale (Demecolcin), Acta haemat.

9. Mikkelsen, W. M.; Salin, R. W., and Duff, I. F.: Alopecia Totalis After Desacetylmethyl-11:280, 1954.
colchicine Therapy of Acute Gout: Report of a Case, New England J. Med. 255:769, 1956.

10. Kuzell, W. C.; Schaffarzick, R. W., and Naugler, W. E.: The Effect of Intravenous Demecolcine (Colcemid) on Acute Gout, A. M. A. Arch. Int. Med. 96:153, 1955.

11. Smyth, C. J.; Huffman, E. R., and Wislon, G. M.: Treatment of Gout, A. M. A. Arch. Int. Med. 97:783, 1956.

Complete Heart Block Due to Syphilis

ALBERT WEINSTEIN, M.D.; R. H. KAMPMEIER, M.D., and T. R. HARWOOD, M.D., Nashville, Tenn.

Complete atrioventricular block of a permanent or intermittent type is a relatively uncommon alteration of conduction. It may develop in the course of acute rheumatic fever and diphtheria. It is most commonly found in elderly persons in association with serious forms of chronic heart disease, usually of a coronary arteriosclerotic type, with or without aortic valvular heart disease. The arrhythmia may also occur in association with congenital heart disease, syphilitic heart disease, and neoplasm. Rarely it appears as a complication of digitalis therapy.

A reflex vagal mechanism as is present in the hyperactive carotid sinus syndrome may account for complete heart block, and this variety is ordinarily evanescent. In episodes of supraventricular tachycardia, atrial flutter, and atrial fibrillation, exhaustion of the conduction system presumably occurs, often resulting in complete atrioventricular dissociation.

When atherosclerosis is the cause of complete block it is usually the right coronary artery which is involved, since the atrioventricular node and bundle is supplied by one of its branches. This branch arises early in the distribution of the right coronary artery. When thrombosis occurs it is usually distal to this branch, therefore atrioventricular dissociation is unusual in right or posterior coronary artery thrombosis, which is so frequently encountered.

In calcific aortic stenosis the proximity of the diseased area to the conduction system often results in conduction changes and, occasionally, in complete block.

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From the Departments of Medicine and Pathology, Vanderbilt University School of Medicine.

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Syphilitic heart disease infrequently may be manifested by complete atrioventricular dissociation. This may occur as the result either of isolated gummata in the atrioventricular bundle, gummatous myocarditis extending from the aorta into the bundle, or of failure of the coronary blood supply to the bundle because of syphilitic stenosis of the ostium of the right coronary artery. We have collected from the literature 18 cases of syphilitic cardiovascular disease in which complete atrioventricular dissociation has occurred and are reporting two additional cases from our own experience.

Report of Cases

CASE 1.—A white woman, age 37, was admitted to the Vanderbilt University Hospital on Jan. 6, 1955, and died on Jan. 20. She entered at 9 p. m., with the complaint of convulsions.

She had not been feeling particularly well during the past year, and especially during the past three months. A swelling in her neck had been noted about three months before admission; this led her to consult a physician. At that time examination revealed a rapid heart, but no irregularities were noted. The basal metabolic rate was reported to be normal, as was an electrocardiogram also done at that time. There had been some exertional dyspnea during the month before admission, and she reported that she had begun to sleep on one pillow. During this month she had had repeated respiratory infections.

Five days before admission she suffered two episodes of fainting ("blackouts") which lasted for several minutes and was reported to have become cyanotic during these attacks. The episodes had occurred daily. At 7:30 a. m. on the day of admission, while driving her automobile, the patient fainted at the wheel. This attack was similar to previous episodes. One hour later there was another attack; at this time she became very pale and had a convulsion which continued for about a minute. Because of the severity of this attack the local fire department was called, and mechanical resuscitation was applied. She was then

Fig. 1.—A 14-second period of ventricular asystole.

admitted to the Jennie Stuart Hospital at Hopkinsville, Ky.

At the time of admission to that hospital she was conscious, her color was reported to be good, and no cardiac abnormalities were noted. About three hours after admission she had an attack which was observed by her attending physicians, Dr. John Garner and Dr. Preston Higgins. They noted that she became pale and pulseless for more than a minute. An electrocardiogram taken during the episode showed a period of ventricular asystole (Fig. 1), with continued auricular activity. She was given atropine and ephedrine at that time, and the convulsive seizure passed, and the pulse rate returned to normal. However, throughout the day she continued to have repeated episodes of fainting associated with convulsions and cardiac standstill. Accordingly, she was transferred to the Vanderbilt University Hospital.

The past history indicated that she had been having headaches during the past year but had had no visual disturbances. She had been married for 17 years. The husband, who accompanied his wife to the hospital, apparently was well. They have one child, the only pregnancy, who was reported to be living and well. The patient did not use alcohol or tobacco. Her father, 72, was living and well; the mother, 67, has angina. There are four brothers and sisters, living and in good health, with the exception of one who was reported to have had rheumatic fever.

Examination.—At the time of admission, the patient was observed to be a well-nourished, apparently healthy woman, lying flat in bed without any respiratory difficulty.

Shortly after admission she had an attack which established a pattern that was followed in the subsequent attacks. The patient would suddenly develop a look of anguish, and her face would become bloodless. The period of remarkable pallor was soon followed by a generalized convulsion, during which time the heart could not be heard and the radial arterial pulsation was gone. After a brief period of time, usually from a few seconds to as long as more than a minute, the pulse would become perceptible, the convulsion would cease, and the face would flush. The dramatic improvement would progress, and she would soon feel perfectly well, would be alert, and would cooperate fully to questioning.

In the intervals between the attacks it was noted that her heart was not enlarged; there were a Grade 2 systolic and a diastolic murmur at the base of the heart; no thrills could be felt; at the apex there was a Grade 1 systolic murmur which had a variable presystolic phase. A systolic thrill was felt over the left carotid artery and the carotid sinus area. Massage of the carotid sinus during intervals when the heart rate was regular caused some perceptible slowing of the heart. This, however, was not marked. The peripheral vessels were not sclerotic; the retinal vessels were normal; the blood pressure was 120/40. There were no rales at the lung bases; the liver could not be felt; there was no edema; pulsations were palpable in the vessels of the feet.

Laboratory Findings.—The urine never showed more than a trace of albumin; the hemoglobin varied between 10.4 and 11.6 gm., the hematocrit, between 33 and 40; the sedimentation rate was constantly elevated to 18 to 26 mm. per hour (Wintrobe method); the differential blood cell count was normal; biochemical determinations were as follows: serum sodium, 143.7 mEq/liter; potassium, 3.8 mEq/liter, and chlorides, 98 mEq/liter. The urine cultures were sterile; six blood cultures revealed no growth. The blood Kahn was doubtful, and the blood VDRL was negative.

Clinical Course.—It was felt that there was probably an abnormal mechanism associated with the carotid sinus reflex. Accordingly, the patient was given rather large amounts of atropine, receiving 0.0008 gm. of atropine and 0.25 gm. of ephedrine every three hours by hypodermic injection. Sodium lactate was not employed.[1]

During the first 24 hours after admission the patient had frequent episodes of cardiac standstill with minor convulsive responses. In the next day or two she became quieter and had a period of three days, from Jan. 8 to 11, during which she had no convulsions. The aortic murmurs became more evident, and the peripheral signs of aortic insufficiency were quite prominent. The collapsing pulse and capillary pulsations were easily visible. The aortic second sound was audible but not accentuated. The systolic murmur at the base of the heart was moderately rough in quality. Following this period of freedom from convulsive episodes the attacks returned, and on Jan. 18 and 19 convulsions occurred every hour or two. On Jan. 29 the attacks continued, and finally, at 6:30 a. m. on that day, there was a sudden episode of gasping, and cyanosis, and, in spite of all methods applied

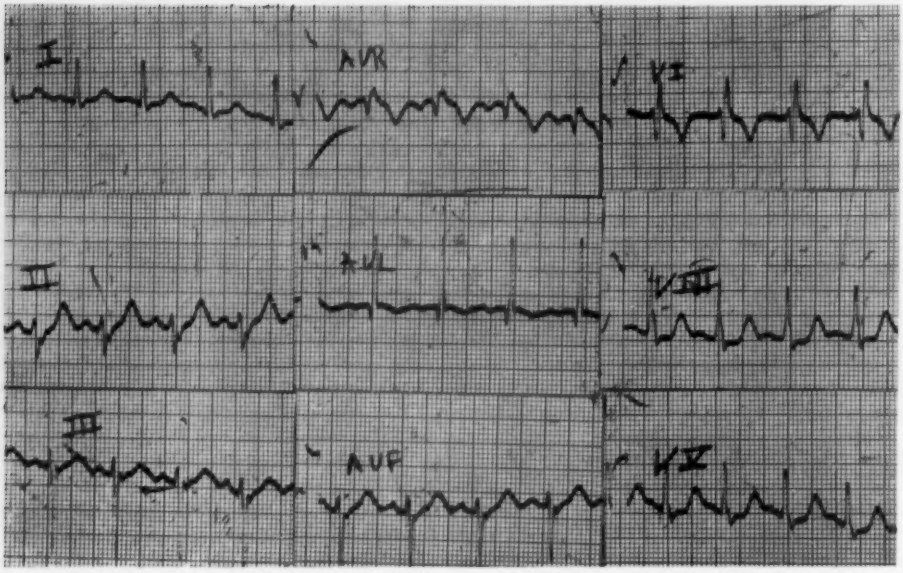

Fig. 2A.—Right bundle-branch block—sinus rhythm.

to restore respiration and the cardiac cycle, the patient failed to respond.

During the stay in the hospital several electrocardiograms were obtained (Figs. 2A and 2B). They all showed varying degrees of complete block, with sinus tachycardia and multiple premature ventricular contractions. At times there were periods of complete standstill. In addition, incomplete right bundle-branch block was present. During an interval when the patient was doing well, fluoroscopic study of the chest showed normal excursion of the lung fields and some suggestion of enlargement of the left auricle. Neither ventricle seemed to be particularly enlarged. A routine

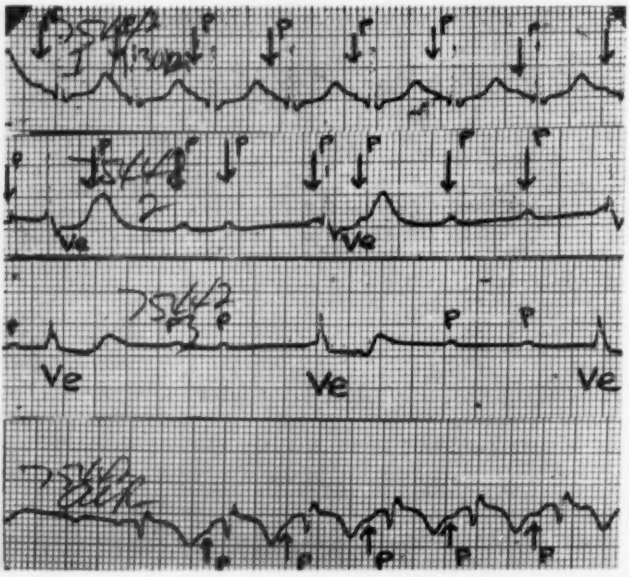

Fig. 2B.—Right bundle-branch block with intermittent failure of auriculoventricular conduction.

chest film showed the cardiac shadow to be within normal limits in over-all size.

The patient was afebrile during the hospital course. However, because her white cell count varied between 14,000 and 23,000, it was felt that she might have rheumatic fever, and accordingly cortisone was given from Jan. 7 until her death. The initial amount was 300 mg.; the dose was then progressively decreased, and after three days she was taking a total of only 75 mg. daily.

Additional Information.—After death and when the autopsy findings were reported, her physicians in Hopkinsville were consulted. A blood sample was obtained from the husband, and it was negative in both the Wassermann and the Kahn tests. Blood from the daughter showed positive Kahn and Wassermann reactions. On further inquiry of her local physicians, it appeared the patient had never received any penicillin to their knowledge, nor had anyone been aware of the presence of syphilis. Accordingly, no other type of antisyphilitic treatment had ever been given by her physicians.

Autopsy Findings (Necropsy by T. R. Harwood).—Gross Examination: The positive gross findings were confined to the heart and major vessels, except for edema and congestion of the lungs and congestion of the liver.

Pericardium: The pericardial surfaces were shiny and smooth. The right pulmonary artery was stenotic, due to encirclement by a yellowish-green rubbery mass of tissue which extended downward around the right coronary artery and into the heart.

Heart: The epicardial surface was smooth and shiny. The myocardium of the major portion of the upper part of the septum, the area of the auriculoventricular node, and portions of the atria were replaced by an opaque white to greenish-yellow rubbery mass, which was continuous with the mass around the right pulmonary and right coronary arteries and extended upward around the base of the aorta. The endocardium was smooth throughout, although the gummatous mass beneath it caused some nodularity. All chambers of the heart were dilated, and on section the muscle appeared coarse. Some fine white mottling was seen in the myocardium.

The valves were all thin and had free edges, except for the aortic valve, which showed slight thickening and sagging, with widening of one of the commissures. The coronary ostia appeared higher in the aorta than usual. The ostia were quite narrowed, measuring only 1 to 1.5 mm. in diameter. The left coronary artery was narrowed for only about 3 to 5 mm. before opening out and remaining widely patent throughout the rest of its course. The right coronary artery was narrowed for about 1 cm. along its course before becoming widely patent.

Aorta: The aorta showed typical "tree-bark" wrinkling of the intima in the ascending part. The ascending aorta and proximal arch were widened and dilated, and cuts across the wall showed loss of media with thickening and an edema-like change of the adventitia, resulting in a rubbery and somewhat friable structure. These changes ended abruptly at the distal arch, and the remainder of the aorta distally had a smooth intima and intact wall. In the proximal arch was an area which on section showed three focal areas of opaque yellow gummy material, the largest being about 0.5 cm. in diameter.

Microscopic Examination: The lesions in the heart, around the coronary and pulmonary arteries, and in the aorta were all similar in nature. Sections from the auriculoventricular node and adjacent septum showed a caseous-like area of necrosis with giant-cell formation and plasma cells. A few degenerating muscle fibers were recognized within the necrotic areas (Fig. 3). Surrounding the inflammatory mass was typical syphilitic granulation tissue composed of newly formed capillaries, proliferating fibroblasts, large macrophages, many plasma cells, and some lymphocytes. Perivascular cuffing was prominent. Most of the necrotic areas in the heart seemed connected, suggesting that all of the heart lesions were part of a single gumma. Levaditi stains failed to show spirochetes.

The aortic lesions were typical of syphilitic mesaortitis in most areas, but in the proximal arch showed focal gummas rather than a single process. Again Levaditi stains were unsuccessful in showing organisms.

The following microscopic diagnoses were made in this case: Syphilitic gumma of the heart, syphilitic aortitis, focal syphilitic pancreatitis, old granulomatous disease of the lungs, and chronic cervicitis with squamous metaplasia.

Comment.—This was the case of a 37-year-old white woman who, after a year of ill-defined impaired health, developed evidence of myocardial insufficiency and then a dramatic onset of repeated attacks of syncope with or without convulsive seizures. These episodes were shown to be due to ventricular asystole, and death occurred in such a period three weeks after their onset. Aortic insufficiency was present. The blood Kahn and VDRL tests were negative. Postmortem examination revealed gummatous

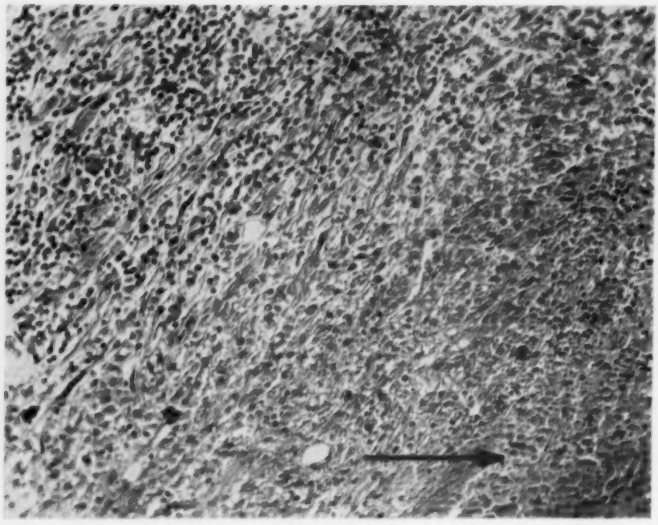

Fig. 3.—Section from margin of gumma. Necrotic zone (arrow) surrounded by area of fibrosis with a heavy infiltration of lymphocytes and plasma cells at the periphery. Myocardial fibers are identifiable in the zone of cellular infiltration.

infiltration of the upper portion of the interventricular septum in the region of the auriculoventricular node and the right pulmonary and coronary arteries, extending around the base of the aorta. The clinical considerations of this patient's condition had not included syphilis in the differential diagnosis.

CASE 2.—A 50-year-old Negro man was admitted to the Vanderbilt University Hospital on June 13, 1932, complaining of dyspnea and fainting spells.

Seven weeks previous to this date he had noted slight dyspnea on exertion, which became so severe that he could walk only a short distance on the level without distress. Ten days before admission vertigo and a sense of substernal fullness were noticed, and the preexisting symptoms became aggravated. These symptoms continued, and the day prior to admission he suddenly lost consciousness while walking. This attack of syncope lasted but a few moments, and upon regaining consciousness he was weak, dyspneic, and flushed. It is interesting that at this time he was arrested for suspected intoxication but was released shortly. On the day of admission a similar attack occurred, accompanied by paraumbilical aching that persisted for hours.

The past history was essentially negative. He had no cough, edema, cyanosis, swelling of the abdomen, or hematemesis. No history of syphilis was obtained; he had had urethritis at the age of 35 and again one month previous to his entrance to the hospital. As a child he was said to have had "scrofula." No history of diphtheria or rheumatic infection was obtained. He had married twice. The first wife had had two living children and one premature child (8 months), who died. The second wife had had no pregnancies. The patient had always done strenuous work in a foundry or on a train repair crew.

Physical Examination.—The physical examination revealed a well-developed and muscled Negro man who appeared exhausted and somnolent. His breathing was rapid and shallow, and the slightest movements were accompanied by dyspnea. The mucous membranes appeared pale, and the tonsils, large and injected. Slight arteriosclerosis was present in the retinal vessels and peripherally. Congestion was evident at the right lung base.

The cardiac dullness extended 6 cm. to the right of the midsternal line and 9.5 cm. to the left in the fifth intercostal space. The apex rate was 30. The auricular rate, as counted from the sounds heard parasternally and the pulsations seen in the dilated cervical veins, was 100. A harsh, blowing, systolic murmur best heard in the mitral area was transmitted to the left axilla. The blood pressure was 98/48. The liver extended 3 fingerbreadths below the right costal margin. There was no evidence of free fluid in the pleural or peritoneal spaces. spaces. The prostate was moderately enlarged, and a purulent urethritis was present.

Laboratory Findings.—Urinalysis showed albuminuria and numerous leukocytes. The red

cell count was 3,600,000; the hemoglobin, 8.4 gm., and the white cell count, 4900; the differential blood cell count was not remarkable. The phenolsulfonphthalein excretion was 53% in two hours. The Wassermann reaction was strongly positive on two occasions, and the Kahn tests were also reported as positive. The blood protein nitrogen was 33.3 mg. on admission and 41.3 mg. per 100 cc. the day before death. An electrocardiogram taken on July 14 showed first-degree heart block, with a P-R interval of 0.36 second, a rate of 50, and a notched QRS in all leads. On the following day the tracing revealed a ventricular rate of 30 and complete dissociation of auricle and ventricle (Fig. 4).

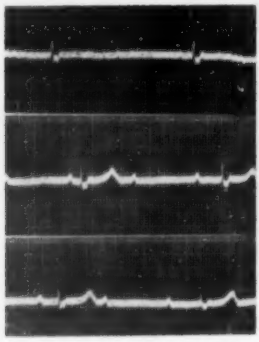

Fig. 4.—Electrocardiogram showing complete auriculoventricular dissociation.

An x-ray film of the chest on June 15 showed a general increase in the heart shadow, which measured 6.7 cm. to the right of the midsternal line and 8.9 cm. to the left. Signs of chronic pneumonitis were present at the right lung base. A fluoroscopic examination of the chest on June 20 showed the auricular rate to be approximately three times that of the ventricle.

Clinical Course.—Five days after admission the following findings were noted. There were moderate dyspnea, tenderness of the liver, and distention of the neck veins. The pulse was weak, and the rate was 28 per minute. An occasional heart sound was louder than the others. No diastolic murmur was heard.

On June 22, the patient complained of smothering spells and of pain in the left lower quadrant that radiated up the left side of the body to the neck. Attacks of paroxysmal dyspnea became frequent and severe. Moderate congestion of the lungs, pitting edema of the ankles, and swelling of the liver to within 2 cm. of the umbilicus were observed at this time. The pulse rate was 30. It was noted that no attacks of syncope had occurred since the onset of complete block on June 15, but that moderate congestive failure had developed.

Ephedrine in a dosage of 0.025 gm. twice daily gave a temporary rise of the diastolic blood pressure but did not increase the pulse rate or induce any clinical improvement. Atropine in doses of 0.001 gm. given by hypodermic caused a slight rise in the systolic blood pressure, but no increase in the pulse rate was noted. No clinical improvement followed.

On the morning of June 23 the pulse rate fell to 17. The patient was orthopneic at this time, and he developed delirium. The pulse became very weak, and he died suddenly.

Autopsy Findings.—Only those positive findings related to the cardiovascular system are reported.

Gross Findings: Pericardial Cavity. The pericardium was easily picked up and incised. There was no increased pericardial fluid, and that which was present was of a normal straw color. The pericardial surface was smooth, a little duller than normal.

Heart. The pulmonary artery was opened. A considerable amount of blood ran from the artery; no emboli were found in the larger branches. The heart weighed 370 gm. and was considerably paler and less firm than normal. The epicardium was smooth, and there were no localized areas of opacity, but the entire epicardium was somewhat duller than normal. A pale creamy yellow ridge of fat lay along the course of the right coronary artery and hid it from view as far as the origin of the right marginal artery. This abnormally prominent ridge of fat was more firm and more of a rubbery consistency than normal epicardial fat. Upon opening the heart the auricular portion of the right atrium was found to be filled with a friable clot separated from the wall only with difficulty. The chamber of the right ventricle was moderately enlarged. A rather firm ridge in the myocardium of the right ventricle beginning at the basilar attachment of the right anterior cusp continued with decreasing prominence along the base of the pulmonary artery to the left attachment of the posterior cusp (Fig. 5). Here the ridge was continuous to the most anterior papillary muscle of the interventricular septum. This papillary muscle was greatly enlarged, but no visible difference was found in the muscle or other papillary muscles. It was slightly firmer and of a more rubbery consistency. This was also true of the ridge along the base of the pulmonary artery. No changes could be made out in the left ventricular myocardium except very near the anterior

Fig. 5.—The right ventricle and auricle opened to show the gumma surrounding the right coronary artery and the mural thrombus in the right auricle. The enlarged papillary muscle described in the gross is also seen in this photograph.

portion of the interventricular septum, where, on opening the chamber, a focal change was found to be present which resembled the cut surfaces of the previously described areas. These ridge areas were rubbery, giving with increased resistance when cut. The cut surface consisted of poorly fibrous tissue streaks of heart muscle. The surface was clean, and no areas of liquefaction were made out.

Aorta. The base of the aorta was markedly thickened by pearly white fibrous tissue proliferation mainly between the aorta and the left auricle, which was also involved. This was continuous with a marked proliferation, which surrounded and constricted the right coronary artery near the orifice and along its course. The coronary artery, near its orifice, appeared as a hard and cartilaginous mass with a radius of about 1 cm. in width. There was slight longitudinal wrinkling of the intima, and there were yellow opaque areas just above the origin of the anterior and right posterior cusps. The right coronary artery was considerably constricted in its entire course to the origin of the right marginal artery. The site of greatest constriction was about 1 mm. from its orifice.

The gross provisional anatomic diagnosis was gumma of heart, involving the atrioventricular bundle and right coronary artery; cardiac dilatation and hypertrophy; aortitis, chronic, syphilitic; thrombus of the heart, mural thrombi of the right auricle.

Microscopic Findings: Heart. Sections from the lesion described in the gross involving the interventricular septum and along the right coronary artery showed a lesion, the central portion of which was composed of caseous material, in which there were only a few fragments of nuclear material scattered in the degenerating collagen fibers. Around the edge and within the edge of this central caseous material were a few giant cells. Surrounding this zone was an area in which many degenerating cells showing pyknotic nuclei were found. In this zone also were a few necrotic muscle fibers. Giant cells were more numerous in and just outside this zone. The giant cells showed the nuclei of giant cells of foreign-body reaction. The necrotic cellular zone was sur-

rounded by another definite zone composed mainly of infiltrating cells, most of which were round cells, though many polymorphonuclear cells were present. The round cells were the large mononuclear type of lymphocytes and plasma cells. Here was the first zone in which the architecture of the myocardium could be made out. Practically all the muscle cells in the cellular zone showed degenerative changes in the cytoplasm with less prominent striations.

The radiations extended into the surrounding myocardium from the cellular zone. The bundles nearest were distorted by interfiber infiltrations. There were only perivascular infiltrations around the small arterioles. This description was of a lesion in the enlarged papillary muscle of the interventricular septum. The lesion differed little from sections taken elsewhere from the affected area. In one of the sections taken from the lesion of the interventricular septum the degenerating zone extended almost to the endocardium. Here the endocardium was thickened and the Purkinje fibers were infiltrated by polymorphonuclear cells.

Sections from the region where the lesion surrounded the coronary artery showed involvement of only the adventitia of the artery, not of the media or intima. The adventitial layer resembled that of the aorta. The small blood vessels incorporated in the lesion and in the vicinity of the lesion showed concentric thickening of the intimal layer, some so much that the lumen was occluded. A few in the outer zones of the lesion showed cellular infiltration, most of the cells being of the round-cell type.

Sections of the heart distant from the gross lesion showed moderate hypertrophy and no cellular infiltration. Many sections stained with Levaditi's method failed to show any spirochetes. Inoculation of fresh myocardium into animals also failed to prove the existence of spirochetes.

The aortic intima showed no thickening. The media was not scarred. The adventitia was considerably thickened by dense collagen fibrils. The small arteries in this layer showed rather striking thickening of the walls, especially of the inner coat. A few small focal areas of round-cell infiltration were present in the thickened adventitia.

Comment.—After some seven weeks of increasing breathlessness, and later some vertigo, this 50-year-old Negro man had an attack of syncope on the street leading to his arrest on the charge of intoxication. A second attack occurred on the day of admission to the hospital, and the third episode, on the 10th day of hospitalization, ended in death. The postmortem examination revealed a gumma of the right ventricular wall, extending into the interventricular septum.

Comment

The first patient was seen in 1932, at a time when syphilis was encountered as a more than everyday event. The second patient was examined in 1955, at a time which might be classified as the postpenicillin spirochetal era. The possibility of syphilis was not readily entertained. The patient was from a good family background, the mother of a healthy 16-year-old daughter, and living with an obviously healthy spouse.

This case is interesting indeed from its clinical course and pathologic background, but it is even more important, as a text, that syphilis even today is not extinct. We must continue to remember the possibility of syphilis in our diagnostic maneuvering. We believe that the "younger" generation of medical students which learns about syphilis from didactic lectures in most medical schools, because of the paucity of clinical material, will be particularly vulnerable in this regard. This is self-evident when those of us who have had considerable experience with this disease in the past did not seriously consider syphilis as a possible cause when the occasion arose.

Generally speaking, syphilis has become a subclinical entity in face of the effectiveness of penicillin. It can be anticipated, however, that in the next 10 to 20 years we will continue to meet the late manifestations of the disease. The acute stage, only, having been controlled, serorelapse and even clinical relapse may go unrecognized, resulting from an inadequate use of penicillin or other antisyphilitic agents. Through an increasing knowledge of the frequency of the incidence of false-positive serologic tests for syphilis, one notes an increasing tendency for those inexperienced in syphilis to disregard even positive tests unless there is an overt history of a genital lesion.

At the time this patient was under our care we did not have available an instrument for external electric stimulation of the heart, as developed by Zoll.[2]

It is our purpose to present merely the clinical entity of atrioventricular dissociation as the result of gummatous invasion of the bundle of His. Its rarity is revealed through the few case reports which have appeared in the literature—to the number of 18.

Gummatous involvement of the myocardium occurs much more frequently but represents, in the main, findings at necropsy. Only rarely may it be diagnosed during life, but might well be suspected at times as in our cases. Sohval,[3] in 1935, reviewed the subject of gumma of the heart. He divided the lesion into two types: (1) diffuse gummatous myocarditis and (2) localized gummatous myocarditis. Of the first he found only seven recorded instances unassociated with the gross localized gumma. The microscopic picture is that of "extensive interstitial and perivascular granulation tissue infiltrated by lymphocytes and plasma cells. Occasionally giant cells are present. There are also obliterative endarterial lesions and frequently miliary areas of coagulation necrosis. These necrotic foci are sometimes of submiliary size, but when larger constitute a stage of transition to the well localized gumma. The myocardial fibers may show atrophy and fatty change. There may be no macroscopic lesions or, at most, innumerable whitish flecks."

Sohval found in the literature 97 instances of localized gumma of the myocardium varying in size from a pinhead to a hen's egg. Most instances occurred in the left ventricular wall, in its upper portion; in some instances the gumma was in the papillary muscles. At times gummas of the myocardium have been found at necropsy incidental to and in no way related to the clinical disease or cause which led to death. In all instances the pathologic process has varied from the necrotic stage, with a surrounding zone of granulation tissue, to more chronic stages, in which the lesion is encapsulated by dense connective tissue with fibrous strands radiating out between the bundles of myocardial fibers. From his survey of the literature, Sohval indicated the circumstances under which cardiac disease may suggest a gummatous etiology. These are (1) ventricular aneurysm in the upper ventricular wall in contrast to the more apical location of an aneurysm due to myocardial infarction; (2) unusual murmurs or combinations of murmurs because of direct invasion of valves or juxtavalvular areas by a gumma of the myocardium producing stenosis to an outflow tract,* and (3) arrhythmias having origin in the atrioventricular conducting system. Other authors have related the electrocardiographic findings of bundle-branch block to gumma of the ventricular wall.

Our two cases are presented as examples of the clinical manifestation of disease of the conducting system in which gumma may be suspected as the etiologic factor. As has been indicated, this is a rare disease in anyone's clinical experience. After meeting the patient studied in 1932, Burwell and Guinand [4] searched the literature with respect to the instances of heart block due to gummatous myocarditis and the association of congestive failure in such cases. They found 15 cases proven pathologically to have a septal gumma as the cause of Stokes-Adams attacks.[4-19] Five showed the clinical picture of congestive failure. In addition to the involvement of the atrioventricular bundle, they had other pathologic changes to account for failure—coronary disease in three, impingement of the gumma upon heart valves resulting in interference with blood flow in three, and ventricular dilatation or hypertrophy in all five instances.

In carrying this study further we have found the reports of a number of instances of myocardial gumma in the subsequent

* In published cases Sohval found an interference with the flow through the aortic valve in 12, pulmonary valve in 13, mitral valve in 2, and in the tricuspid valve in 5 instances, some of these as combined findings in the same case.

years. Among these have been an additional three cases of atrioventricular dissociation,[20,21] two having had Stokes-Adams syncopal attacks. Congestive failure was present in two. One of these patients had been under prolonged treatment for arteriosclerotic heart disease. The other had extensive syphilitic involvement of the pulmonary artery. All three of these reported cases had gross gummatous disease of the interventricular septum upon pathologic examination.

Our recent case, which stimulated this report, presented a finding which deserves additional comment. She was found at necropsy to have three gummas, grossly observed, in the aortic wall. Gummatous aortitis was made the subject of a paper by Gordon, Parker, and Weiss,[22] in 1942. In a total of 360 cases of syphilitic aortitis studied, from the Boston City Hospital and the Massachusetts General Hospital, they found microscopic gummas in 8 (a ratio of 1:45). These authors reported 3 instances of macroscopic gumma of the aorta and say that including their cases the total number of adequately described cases of this lesion do not exceed 10. They make the statement that no instances of gummatous aortitis have been described in which there was an accompanying gummatous myocarditis and that in no instances of reported gummas of the myocardium has there been also gummatous disease of the aorta. If this be true, our Case 1 is the first example of this combination of gummatous lesions.

Summary

Two patients suffering from the Stokes-Adams syndrome on the basis of gummatous disease of the interventricular septum are added to the 18 reported cases in the literature.

One of our patients brings to seven the number of this group who also presented congestive failure.

The other patient had macroscopic gummas of both the aorta and the myocardium, a combination of lesions hitherto thought not to occur.

At the present, although syphilis is a disease of historical importance primarily, it cannot be overlooked as a cause of illness, and Osler's advice, "Know syphilis and you know medicine," still stands.

Vanderbilt University School of Medicine, Department of Medicine (5) (Dr. Kampmeier).

REFERENCES

1. Bellet, S.; Wasserman, F., and Brody, J. I.: Treatment of Cardiac Arrest and Slow Ventricular Rates in Complete A-V Heart Block: Use of Molar and Half Molar Sodium Lactate; a Clinical Study, Circulation 11:685, 1955.

2. Zoll, P. M.; Linenthal, A. J., and Norman, L. R.: Treatment of Stokes-Adams Disease by External Electric Stimulation of the Heart, Circulation 9:482, 1954.

3. Sohval, A. R.: Gumma of the Heart: Report of 2 Cases, Arch. Path. 20:429, 1935.

4. Burwell, C. S., and Guinand, P. H.: Personal communication to the authors.

5. Turner: Case Report Before Hunterian Society, Brit. M. J. 1:667, 1890.

6. Rendu, M.: Note sur un cas de syphilis du cœur, accompagnée de pouls lent permanent, Bull et mém. Soc. méd. hôp. Paris 12:381, 1895.

7. Handford, H.: Remarks on a Case of Gummata of the Heart, Brit. M. J. 2:1745, 1904.

8. Keith, A., and Miller, C.: Description of a Heart Showing Gummatous Infiltration of the Auricular Ventricular Bundle, Lancet 2: 1429, 1906.

9. Ashton, T. G.; Norris, G. W., and Lavinson, R. S.: Adams-Stokes Disease (Heart block) Due to Gumma in the Interventricular Septum, Am. J. M. Sc. 133:28, 1907.

10. Robinson, G. C.: Gumma of the Heart from a Case Presenting the Symptoms of Adams-Stokes Disease, Bull. Ayer Clin. Lab. 4:1, 1907.

11. Vaquez and Eisman: Maladie de Stokes-Adams par lésion scléro-gommeuse du faisceau de His (herz-block), Presse méd. 15:57, 1907.

12. Heineke, A.; Müller, A., and von Hösslin, H.: Zur Kasuistik des Adams-Stokes'schen Symptomkomplexes und der Überleitungsstörungen, Deutsches Arch. klin. Med. 93:459, 1908.

13. Holterdorf, A.: Herzsyphilis mit Adams-Stokes'schen Symptomenkomplex, ausgezeichnet durch Tausende von epileptiformen Anfällen, München med. Wchnschr. 63:1651, 1916.

14. Bridgman, E. W., and Schmeisser, H. C.: Heart Block Caused by Gumma of the Septum, Johns Hopkins Hosp. Rep. 18:90, 1919.

15. Girdwood, R. L.: Gumma of the Heart with Stokes-Adams Syndrome, South. African M. J. 16:186, 1921.

16. Major, R. H.: Stokes-Adams' Disease Due to Gumma of the Heart, Arch. Int. Med. 31:857, 1923.

17. Clarke, N. E., and Smith, F. J.: Heart Block of Unusual Etiology, Am. J. M. Sc. 169:882, 1925.

18. Cleland, J. B.: Gumma of the Interventricular Septum of the Heart Giving Rise to Heart Block, M. J. Australia 1:540, 1927.

19. Kux, E.: Myocarditis gummosa mit Adams-Stokes'schen Symptom-Komplex und Mesopulmonitis luetica, Ztschr. Kreislaufforsch. 24:1, 1932.

20. Spain, D. M., and Johannsen, M. W.: Three Cases of Localized Gummatous Myocarditis, Am. Heart J. 24:689, 1942.

21. Coelho, E., and d'Oliveira, A.: Syphilis de la cloison intraventriculaire et tachycardie ventriculaire: Syphilis de l'artere pulmonaire, Arch. mal cœur 32:17, 1939.

22. Gordon, W. H.; Parker, F., Jr., and Weiss, S.: Gummatous Aortitis, Arch. Int. Med. 70:396, 1942.

Widespread immunization against smallpox, typhoid fever and diphtheria plus the prompt use of antibiotics in other infections has reduced the incidence of epidemic infectious diseases to the point that physicians are becoming careless in the use of infectious precautions and management of known contacts. The two reports which follow will serve as timely reminders of our frequent deficiencies in these respects. The suggestion of "an infection control officer" for every hospital is a good one.

PAUL S. RHOADS, M.D., Chief Editor

Observations on an Outbreak of Infectious Hepatitis

Failure to Apply Accepted Control Measures

MAJOR ALOIS PECZENIK (MC) and CAPT. DAVID W. DUTTWEILER (MSC), U. S. Army

Introduction

That the gap between our knowledge of the control and management of communicable diseases and our application of that knowledge is widening has become increasingly apparent. A recent editorial[1] has pointed out that patients often acquire infections of some type or other during their stay in the hospital and that "the incidence of such infections cannot be stated, because, unlike the weather, nobody talks about it." The truth of this statement will be affirmed by the alert clinician and knowing epidemiologist alike. The survey presented by Colebrook[2] is an insight into the extent and magnitude of this rarely discussed problem, which more often hinges on diligent application of established procedures than on the expensive and lengthy development of complex techniques. Recent experiences of the authors have emphasized this impression with respect to a comparatively new disease among those considered to be communicable: infectious hepatitis. The purpose of this paper is to add an important viral disease to the lengthy list of already known infections which have been incriminated in hospital-acquired infections.

The pages of numerous medical journals and standard references contain discussions of the importance of this disease to the community, whether civilian or military. (An excellent review of the more recent literature has been compiled by Warren.[3]) Presumably the members of the medical profession are well indoctrinated in its treatment and prevention and are aware of the control measures that must be applied when cases appear. Unfortunately, as will be illustrated here, the physician treating a case of infectious hepatitis, or other infectious disease, often fails to realize its importance to the health of the other members of the community and thereby unwittingly contributes to the spread of the disease; more rarely and tragically, an epidemic results.

Several factors contribute to the average physician's attitude. Infectious hepatitis, despite its appropriate name, does not provoke the concern that it warrants. Until very recently, even teaching institutions questioned its degree of infectiousness and the need for isolation of hepatitis patients. Often it has been easy to become accustomed to the usual incidence of the disease and become little alarmed when a "few more than usual" cases appear. Because of the relatively long incubation period, hepatitis

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Preventive Medicine Officer (Major Peczenik) and Assistant Preventive Medicine Officer (Capt. Duttweiler), Office of the Chief Surgeon, Hq., U. S. Forces in Austria.

Present addresses: Chief, Preventive Medicine Service, Fort Jackson, S. C. (Major Peczenik), and The Johns Hopkins University, Baltimore (Capt. Duttweiler).

cases secondary to one under treatment often do not, to the casual observer, appear to be related; a smouldering epidemic, propagated by person-to-person spread, frequently remains undetected unless a thorough investigation is made. Insufficient attention has been given in professional publications, and even less in media that reach the layman, to the long, expensive period of hospitalization and convalescence for each case of infectious hepatitis and the not-infrequent residual liver damage. Consequently, when a case of infectious hepatitis appears, those responsible for medical care do not receive the "pressure" from the public that they would when a case of poliomyelitis occurs, to cite a commonly occurring example. Like it or not, it must be admitted that such "pressure" centers attention on a problem which, with infectious hepatitis, requires prompt, thorough investigation followed by sound action.

The outbreak described here will illustrate and emphasize the fact that infectious hepatitis is a highly infectious disease demanding careful treatment and management in the hospital, together with adequate epidemiologic investigation and subsequent "follow-up" if additional cases are to be prevented. We do not propose to present a classical epidemiologic study of an infectious-disease outbreak. However, we will attempt to outline a chain of events that led to the occurrence of a substantial number of cases and will give special emphasis to failures in the institution of accepted protective measures. Though it is painful to admit mistakes, it is our sincere belief that considerable benefit is to be gained from the recognition of past errors and omissions and that, like the weather, it should be talked about.

Investigation of Outbreak

It serves no purpose to identify the locale or hospital involved. The population served by the hospital consisted of approximately 2600 persons, including military personnel, dependents, and civilian employees. The number of cases of infectious hepatitis for the years 1953-1955 is shown by month in Table 1. It is generally thought that the "normal" incidence, i. e., that of 1953 and 1954, was the result of person-to-person spread, perhaps through contact with unrecognized cases.

The outbreak occurred during the four months April-July, 1955. Unfortunately, we were able to undertake only a limited investigation of the outbreak at the scene after it had subsided. The investigation was conducted in September, 1955, and consisted of the study of the clinical records of the cases and detailed questioning of the patients if they were adult or older children; in cases of young children, one or both parents were interviewed. A specially designed questionnaire was personally completed by us on every case. However, preliminary review of routine reports for each admitted case of infectious hepatitis, together with study of daily hospital admission and disposition reports, had yielded considerable pertinent information. Especially noted was the large proportion of cases in individual families (Family "A," five cases among seven members; Family "B," three cases among four members) and the number of cases in children. In addition, it was discovered that two cases who had been hospitalized for minor surgical conditions together with an acute case of hepatitis on an open ward showed symptoms of the dis-

TABLE 1.—*Cases of Infectious Hepatitis in the Outbreak Area in the Years 1953, 1954, and 1955* *

Year	Jan.	Feb.	March	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Total
1953	2	1	0	2	0	1	0	1	1	1	1	0	10
1954	1	1	1	1	1	1	0	1	1	2	0	0	10
1955	0	0	1	8	3	3	6	0	0	2	1	0	24

*This table is based on date of admission to treatment, in accordance with military morbidity reporting procedures. Table 2 and the Figure are based on date of onset of symptoms. For this reason, the reader will not be able to reconcile from these sources the number of cases for certain months.

ease approximately one month after admission to this ward.

Investigation of the affected installation produced the total number of confirmed cases of infectious hepatitis during the period March 1-July 31, tabulated in Table 2. Of the total of 20 cases considered in connection with this outbreak (Case 1, the only other case since the beginning of the year, is not included but is shown in Table 2 and the Figure for completeness), 14 were found to have at least suspicious epidemiologic connection. Of the remaining six cases, two (Cases 19 and 20) were found to have acquired the infection outside the area of the outbreak and one (Case 7) was found to have been a close contact of a chronic hepatitis case; finally, three (Cases 6, 14, 18) were found to have no credible connection with other cases but had probably acquired the infection within the area of the installation.

As shown in Table 2, the first four connected cases (Cases 2, 3, 4, 5) were school-age children, with dates of onset within a 10-day period. It seemed distinctly possible that all four initial cases had been exposed to a common source of infection, possibly at their school through some breakdown in the environment, perhaps an infected food handler. The investigation was pursued along this line and produced as incidental information that a female attendant in the school cafeteria utilized by these cases had been treated for general malaise and vague abdominal complaints since early March, 1955. She had not received an intensive gastrointestinal work-up, and no definite diagnosis had been made. Unfortunately, at the time of the investigation, this certainly suspicious person was no longer available. Therefore, it could only be assumed that the initial four cases had acquired the infection in a common manner. Entirely circumstantial evidence pointed to a food handler as the possible source of these initial cases.

A study of the distribution of dates of onset of symptoms for the remaining cases and the obvious familial contact of some with the initial cases, together with other evidence of contact with these cases, led to the conclusion that Cases 8-13, 15-17, and 21 were linked by person-to-person contact to the initial four cases of this outbreak.

Factors Contributing to Spread of the Disease

One of the outstanding aspects of the outbreak is the fact that four cases (Cases 2, 3, 8, 18) were never admitted to the hospital and were treated merely as out-

TABLE 2.—*Individual Cases of Infectious Hepatitis in the Outbreak Area March 1-July 31, 1955*

Case*	Case Families	Age, Yr.	Sex	Date of Onset	Admission to Hosp.	Disch.	Convalescent Leave, Days	Effective Hosp. Period, Days†
1		21	M	March 15	March 22	April 8	0	17
2	A	10	M	March 25	Never			0
3	A	8	F	April 1	Never			0
4	C	11	M	April 2	April 7	April 16	0	9
5	A	12	M	April 3	April 9	April 29	0	20
6		34	M	April 8	April 13	May 28	9	35
7		23	M	April 10	April 13	May 28	0	45
8	C	6	F	April 11	Never			0
9		15	M	April 20	April 25	May 20	0	25
10	A	34	M	April 30	May 3	June 2	16	14
11	A	31	F	May 1	May 6	May 11	0	5
12		20	M	May 12	May 13	June 17	0	35
13	B	34	M	June 2	June 3	July 16	9	34
14		24	M	June 8	June 13	June 30	9	8
15		27	M	June 19	June 22	Aug. 5	9	35
16	B	4	M	June 29	June 30	July 8	0	8
17		24	M	July 5	July 11	?	?	?
18		7	F	July 10	Never			0
19		21	M	July 11	July 20	Aug. 13	9	15
20		24	M	July 15	July 22	Aug. 11	9	11
21	B	8	M	July 16	July 21	July 25	0	4

*All cases of Caucasian race.
†Total period of hospitalization less convalescent leave, which was granted immediately prior to discharge.

patients, not without serious results. Cases 2 and 3, who were allowed to remain in their home during a period of presumably greatest communicability, undoubtedly infected their parents, Cases 10 and 11. The inept handling of these cases may be attributed to inadequate diagnostic procedure, coupled with a failure on the part of the examining medical officer to realize the possible effects of faulty diagnosis or improper management. As an example, Case 2, when first seen in Outpatient Service on April 12, "appeared somewhat icteric" with not other objective findings. The reported laboratory findings at this date were as follows: thymol turbidity, 10 units; cephalin flocculation, 2+ (24 hours), 3+ (48 hours); and serum bilirubin (presumably total), 2.3 mg. per 100 cc. One week later the patient was again examined, was found to be "entirely negative," and was cleared for return to school. It is significant that clearance was granted without further laboratory tests. Though the final diagnosis in this case was infectious hepatitis, no apparent considerations were given to either infectiousness or control measures, and a possibly still-infectious case was allowed to return to normal activities solely because he was asymptomatic.

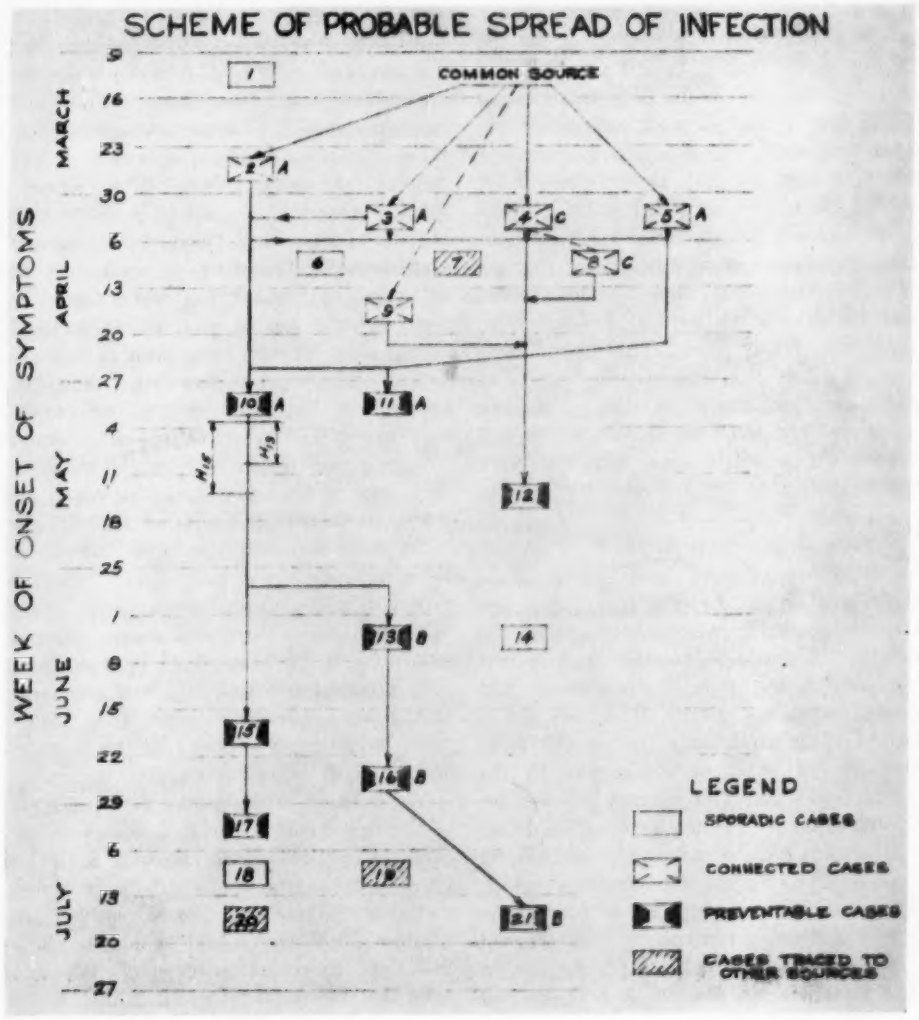
Closely associated with the failure to admit cases of infectious hepatitis to the hospital were the unusually short effective periods of hospitalization for other cases, as can be seen in Table 2. It appeared distinctly possible that Case 21 had acquired the infection through contact with his brother, Case 16, who had been hospitalized only eight days. Again, the patient had been cleared solely on the basis of disappearance of symptoms, without appropriate liver-function testing. It also appeared likely that Case 12, who was a school-bus monitor and had fairly intimate contact with many school children, had been infected through contact with one or several of the cases who either had not been hospitalized or had been discharged after short hospitalization.

It was found that in at least one case (Case 10), management within the hospital apparently contributed to the spread of the infection to other patients. Case 10 was hospitalized in "semi-isolation" in a portion of a large open male ward with practically nonexistent isolation facilities. No aseptic nursing technique was practiced; bedpan sterilization was poor; the patient and attendants had apparently received no instruction in necessary precautions, such as thorough handwashing or other personal hygiene measures, to prevent spread of the disease. Capps et al.[4] have shown how deficient nursing procedures had caused an outbreak of infectious hepatitis among student nurses in an infants' orphanage and how enforcing aseptic nursing technique alone had abolished the outbreak. This failure in nursing technique was considered sufficient evidence to account for Cases 13 and 15 as cases of cross infection who were concurrently present in this ward and were cared for by the same attendants; their dates of onset were 26-30 days and 36-47 days, respectively, after their first stays in the ward. It is particularly tragic that Case 13, before his readmission to the hospital, probably infected his son, Case 16, who in turn infected his brother, Case 21, as cited above. Case 15 was the probable source of Case 17, who were close unit contacts.

The probable "chain of infection" is shown graphically in the Figure. The solid lines connecting individual cases indicate personal contact where the available epidemiologic evidence clearly incriminated this manner of spread. The dashed lines indicate such contact where the available evidence was not so conclusive. The notations H_{13} and H_{15} indicate the periods when Cases 13 and 15 were hospitalized for other conditions together with Case 10.

Comment

Each case of hepatitis, when first seen at the hospital, had been interviewed to determine names of contacts in order to complete a routine report (Individual Epidemiological Case History) required in this military



theater for each case of certain communicable diseases. However, no further epidemiologic effort was attempted by the hospital staff, nor was any action taken on the basis of the available information to prevent spread of the disease. There was in effect at the time of this outbreak a policy that all intimate contacts of cases of infectious hepatitis receive a prophylactic injection of 3 cc. of immune serum globulin. This practice had proven to be effective in preventing secondary cases among intimate contacts of cases and has generally been adopted as a control measure in outbreaks involving orphanages, schools, and other institutions [5] and military organizations.[6] The increased risk of contracting the disease for members of the household of a primary case is well known [7] and is also evidenced by the number of familial cases in this outbreak and by the mode of spread within the family units, e. g., Cases 13, 16, and 21. Despite strong indication for the administration of γ-globulin, this was not done. The authors are convinced that prompt administration of globulin would have prevented

most of the secondary cases, especially those in the afflicted families. A glance at the Figure shows plainly that if Case 10 had been prevented by the use of globulin, Cases 13, 15, 16, 17, and 21 most probably would never have occurred. If intimate contacts of the first four outbreak cases (Cases 2-5), two of which were never hospitalized, would have received prophylactic γ-globulin administration, the possibility existed that the chain of spread could have been interrupted and that all or at last some of the subsequent eight connected cases could have been avoided. Adequate clinical investigation of the suspected school cafeteria attendant could possibly have precluded the entire outbreak. Cases which were judged to have been preventable are indicated as such in the Figure.

As has already been stated, the treatment as outpatients of some cases, and the short periods of hospitalization for others, appeared to contribute to the spread of the disease. It should be pointed out here that current Army policy[6] presumes that hepatitis patients remain infectious for a period of approximately four weeks from the date of onset of symptoms. In the interest of successful therapy of the individual case it is generally recognized that restriction of undue activity or exertion is necessary as long as acute symptoms persist. Thus it appears that a period of four weeks hospitalization (without "convalescent leave") is desirable to protect the patient and his contacts. Regardless of length of hospitalization, discharge should not be based on disappearance of symptoms alone, but on a criteria of sufficiently improved liver function as indicated by sulfobromophthalein (Bromsulphalein) retention, serum bilirubin, and other reliable liver function determinations. Use of such criteria will effectively decrease the number of still infectious but asymptomatic patients from returning to their normal activities, possibly with results such as those described.

It is important to realize that hospital-acquired infections are not a thing of the past, abolished by the work of Semmelweis and Lister in the last century, but that they still constitute a very real problem in operating rooms,[8] nurseries,[9] and medical and surgical wards.[10] Though factual reports in the literature on this topic, especially in this country, are scarce, they are, as Cruickshank[11] reminded, "comparable to the visible part of an iceberg, much more remaining undisclosed." Therefore, it would appear that much more diligent attention should be given to the purportedly well-understood management of infections in the hospital. Colebrook[1] proposes that larger hospitals appoint an "infection control officer"—a sort of house epidemiologist—who would investigate any instance of hospital infection that came to his notice and who would attempt to determine its possible cause and recommend corrective measures. Each year he would prepare a factual and impartial report upon the hospital's success or failure in avoiding cross infections and recommend any reforms he believed to be necessary. This proposal may well be worth consideration in smaller hospitals where cross infections have been a problem in the past, as well as in all larger institutions.

We hope to have shown by the example of this minor outbreak of infectious hepatitis that the patient with hepatitis must be treated in accordance with the accepted methods of infectious disease management if others, both within and without the hospital, are to remain unaffected. We also hope that the emphasis given in this report to failures rather than accomplishments will stimulate future inquiry in that direction, which may eventually produce a solution to this grave hospital dilemma.

Summary

A small outbreak of infectious hepatitis is described. The available evidence indicates that the outbreak was propagated by person-to-person spread facilitated by failure of the medical authorities to apply accepted methods of control. Appropriate control measures are discussed insofar as

they apply to the specific situation, including the adequate utilization of laboratory procedures as criteria for diagnosis and recovery, the necessity for hospitalization of all cases under proper isolation management for an adequate period of time, and the prompt use of immune serum globulin for the prevention of secondary cases. A scheme is evolved of the probable spread of the infection, and the possible effectiveness of accepted but not implemented control measures in preventing most, or at least part, of the cases is hypothesized.

Chief, Preventive Medicine Service, Fort Jackson, S. C.

REFERENCES

1. Infections Occurring in the Hospital, Editorial, J. A. M. A. 160:290 (Jan. 28) 1956.

2. Colebrook, L.: Infection Acquired in Hospital, Lancet 2:885-890 (Oct. 29) 1955.

3. Warren, W. R.: The Epidemiology of Infectious Hepatitis, U. S. Armed Forces M. J. 4:313-335 (March) 1953.

4. Capps, R. B.; Bennett, A. M., and Stokes, J., Jr.: Endemic Infectious Hepatitis in an Infants' Orphanage: I. Epidemiologic Studies in Student Nurses, A. M. A. Arch. Int. Med. 89:6-23 (Jan.), 1952.

5. Stokes, J., Jr.; Farquhar, J. A.; Drake, M. E.; Capps, R. B.; Ward, C. S., Jr., and Kitts, A. W.: Infectious Hepatitis: Length of Protection by Immune Serum Globulin (Gamma Globulin) During Epidemics, J. A. M. A. 147:714-719 (Oct. 20) 1951.

6. Viral Hepatitis, TB MED 206, Army Department, 1954.

7. Dorland, J. D., and Hanlon, R. C.: Epidemic Infectious Hepatitis in a Small Iowa Community, Am. J. Hyg. 43:315-325, 1946.

8. Lowbury, E. J. L.: Cross-Infection of Wounds with Antibiotic-Resistant Organisms, Brit. M. J. 1:985-990 (April 23) 1955.

9. Rogers, K. B.: The Spread of Infantile Gastro-Enteritis in a Cubicled Ward, J. Hyg. 49:140-151 (June-Sept.) 1951.

10. Rountree, P. M.: Streptococcus Pyogenes Infections in a Hospital, Lancet 2:172-173 (July 23) 1955.

11. Cruickshank, R.: Hospital Infection: Historical Review, Brit. M. Bull. 2:272-276, 1944.

A Preventable Outbreak of Poliomyelitis

MAJOR ALOIS PECZENIK (MC) and CAPT. DAVID W. DUTTWEILER (MSC), U. S. Army

Introduction

Poliomyelitis was not a serious problem during the 10-year existence of U. S. F. A. (United States Forces in Austria) as a small military theater in the heart of Europe. Incidence in both military and dependent populations was always sporadic, with the exception of an outbreak during the summer of 1951, when 20 cases were reported in children of the American community at Salzburg, Austria, the command's largest station. Previous incidence of the disease in the area of the outbreak described here was low, with an average of three cases recognized annually during the years 1950-1954. The majority of these cases occurred in school-age children, were mildly paralytic, and rarely left residuals. However, there also were a few cases in young military personnel.

The primary purpose of this paper is not an orthodox epidemiological treatise on a very minor outbreak, but a frank discussion and analysis of possible mistakes in the epidemiologic approach to and medical management of the initial or "herald case." W. H. Frost wrote in the introduction to the American reprint of John Snow's classic on cholera: "Epidemiology . . . is something more than the total of its established facts. It includes their orderly arrangement into chains of inference which extend more or less beyond the bounds of direct observation." It is hoped that the inferences made in this paper have not gone too far beyond these bounds.

The outbreak area had one of the command's finest posts and good living conditions. Troops were stationed at a camp in permanent barracks erected by the German Wehrmacht. Dependent families were housed in six different housing areas of permanent construction, each in a different direction and about 10 miles distant from the camp. Environmental conditions in the entire area were always very favorable and well supervised.

The unusual interest that this small outbreak generated in the command may be attributed to the intensified poliomyelitis consciousness in general and in particular to the "Salk Vaccine" controversy that was in progress at the time. The impending phase-out of the theater due to the signing of the Austrian State Treaty may have accentuated already existing fears. Some of the actions, the attempted mass administration of immune serum globulin for example, were taken under pressure and for their psychological impact rather than for any expected benefits.

Description of the Outbreak

There were eight cases of suspected poliomyelitis from the outbreak area hospitalized during the period May 11 to June 17, 1955. Only five of these cases could be confirmed clinically or by laboratory procedures as poliomyelitis. Ages of the cases ranged from 2 to 7 years; four were paralytic, of which one was of the bulbospinal type; one was nonparalytic. Epidemiological features of these cases are summarized in the Table according to dates of onset of symptoms.

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Present addresses: Chief, Preventive Medicine Service, Fort Jackson, S. C. (Major Peczenik) and The Johns Hopkins University, Baltimore (Capt. Duttweiler).

Preventive Medicine Officer (Major Peczenik) and Assistant Preventive Medicine Officer (Capt. Duttweiler), Office of the Chief Surgeon, Hq., U. S. Forces in Austria.

Poliomyelitis Cases in the Outbreak Area—United States Forces in Austria, May-June, 1955

Case	Sex	Age	Date of Onset of Symptoms	Date of Hospitalization	Housing Area	Poliomyelitis Type	Contacts
*I	F	6½	April 29	T&A May 6-13; polio none	B	Paralytic, spinal (left leg)	1,2
1	M	4	May 10	May 11	B	Paralytic, spinal (neck, both legs)	I
2	F	5	May 23	T&A May 4-7; polio May 25	H	Paralytic, bulbospinal (swallowing, neck, right leg)	I 3,4,5
3	M	7	May 29	June 8	H	Paralytic, spinal (left leg)	2,4
4	M	2½	May 31	June 9	H	Nonparalytic	2,3
5	F	2	June 14	June 17	B	Paralytic, spinal (both legs)	2

*Missed initial case.

Initial Epidemiologic Investigation

All cases were initially investigated by an Army Health Nurse, who completed an "Individual Epidemiological Case History" routinely required in this theater on certain infectious diseases and an additional questionnaire especially designed by her for these cases. This investigation revealed that the cases had occurred in two of the six housing areas; that all quarters were neat and well maintained and revealed no obvious sanitary deficiencies, and further, that one case (Case 2) may have been exposed to a case of poliomyelitis while hospitalized at the local hospital for a tonsillectomy and adenoidectomy. This latter morsel of epidemiological information was somewhat obscured by other aspects of the situation and was not further pursued. It was the consensus of all concerned at that time that the outbreak was not of alarming proportions.

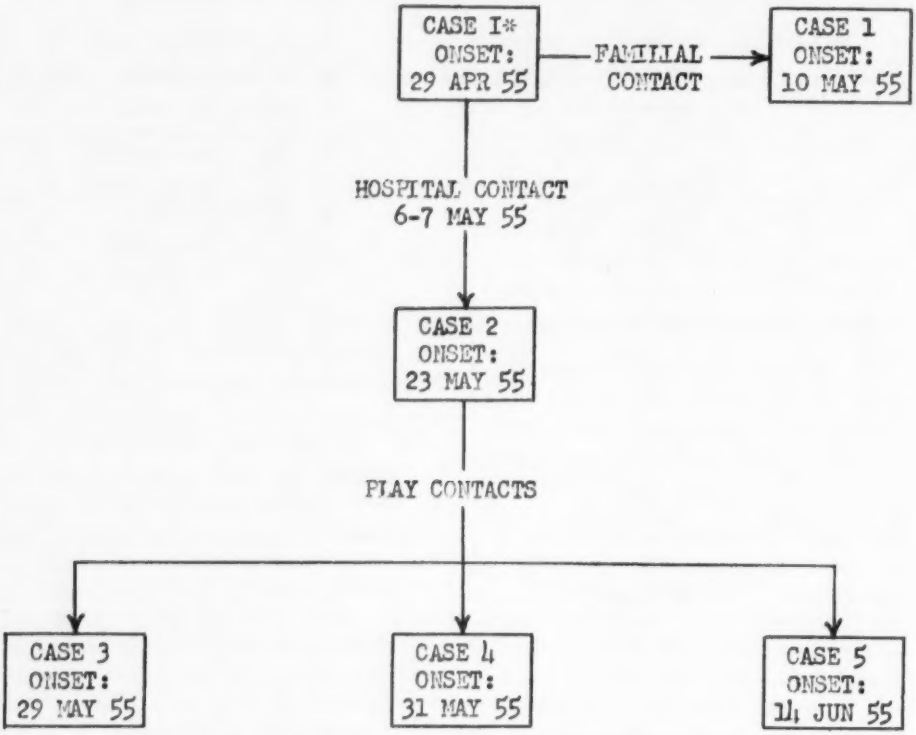
Control Measures

Poliomyelitis globulin was offered on a voluntary basis (May-June 1955) to all pregnant women and to children aged 1-16 years, in a dosage of 0.2 cc. per pound of body weight. The globulin was given with the understanding that "it will do no harm and may do some good." Instructions for accepted and practicable control measures were emphasized and widely disseminated through bulletins and radio; no measures were included that would interfere with normal living routine or contribute to added hysteria. Approximately 12% of the dependents eligible for poliomyelitis globulin administration availed themselves of the offer during June 24-28, 1955, receiving an average dose of 10.5 cc.

Epidemiologic Follow-Up

This outbreak was further investigated by the Preventive Medicine Officer of the command, in that all available epidemiologic data and medical records were reviewed, and the clinical aspects of these cases were discussed with the attending physicians. Epidemiologic investigation was directed toward the objective of determining any possible connection between the cases. The following features could eventually be ascertained.

1. A sister (Case I) of the first recognized case (Case 1) was admitted to the local U. S. Army Hospital for a tonsillectomy and adenoidectomy on May 6 and discharged following completion of this procedure, on May 13. (The practice in this theater to discontinue elective surgical procedures in children between June 1 and Oct. 31, caused a relatively large number of hospitalizations for tonsillectomies and adenoidectomies during the month of May.) Her brother (Case 1) was admitted with clinical signs of the disease on May 11. At that time the attending physician, aware of the familial connection, discovered that the girl (Case I) who had already had the tonsillectomy and adenoidectomy done, showed a slight limp. Upon questioning the parents, he evoked a typical history of mild paralytic poliomyelitis, seven days prior to admission, with gastrointestinal symptoms, headache, sore throat, slight fever, and even some



Scheme of probable case transmission. Asterisk indicates missed initial case.

weakness of the left leg. Therefore, this child who did not manifest sufficiently severe symptoms that would have led to medical attention and recognition of the true illness, may be presumed to have been the first case in that family.

2. The first recognized case (Case 1) probably contracted the disease from his sister (Case I) as a familial contact.

3. The second overt case, Case 2, was hospitalized for a tonsillectomy and adenoidectomy during the period May 4-7 at the U. S. Army Hospital and had been in a bed adjoining Case I for two days. This case, too, was possibly a secondary case of Case I, who was apparently infectious at the time of her operation.

4. All three subsequently hospitalized cases (Cases 3, 4, and 5) were found to be close contacts of Case 2. The impression that they acquired the disease through contact with that child is strengthened by the dates of onset of their symptoms.

In summary, the probable mechanism of transmission involved in this outbreak, shown graphically in the Figure, may be postulated as follows: Case I, the unrecognized or missed poliomyelitis case, infected her brother (Case 1) at home, and infected her bed neighbor (Case 2) at the time of her hospitalization for tonsillectomy and adenoidectomy. Case 2 in turn caused three additional infections among her playmates.

Comment

When the physician attending Case I recognized in her a missed case of paralytic poliomyelitis, he recommended 14 days quarantine for all seven children exposed to that child on the same ward. Though "quarantine" of large groups is impractical and of dubious value, its enforcement in this spe-

cific situation would have been absolutely sound. If quarantine was considered as a too stringent measure, some modification of this method could have been implemented, such as daily medical check-ups (at home by the visiting health nurse) and restriction of these children's activities. Such a procedure could have broken the chain of spread and could possibly have prevented the three secondary cases that may be traced directly to Case 2, a patient from this ward. Furthermore, prophylactic poliomyelitis globulin administration was not promptly given to the exposed seven children on the children's ward, though prophylactic administration of the globulin to selected intimate contacts was in accord with up-to-date preventive practice at that time and was a requirement in this theater. Though it is admitted that the protective capacity of the globulin may have been controversial, its use appeared better indicated at the time of the unhappy discovery that a missed poliomyelitis case had been hospitalized on an open children's ward together with seven tonsillectomy and adenoidectomy cases (Case 2, the child in this group, was actually the only case in the outbreak who developed paralysis of the bulbospinal type) than six weeks later as an abortive attempt at mass prophylaxis. If the poliomyelitis globulin contained any protective qualities, it may have been effective in Case 2, who would have received it in the earliest stage of the incubation period. In that event the possibility existed that all cases, with exception of Case 1, who already had been hospitalized with the acute disease, could have been prevented.

A recent editorial in *The Journal of the American Medical Association*, entitled "Infections Occurring in the Hospital,"[1] revived the interest in hospital cross infections. It discussed the work of Colebrook,[2] who introduced his survey of hospital-acquired infections with these words:

> We are so accustomed to think of the conquest over infectious disease during the past 100 years as a wonderful triumph (as indeed it is) that we are apt to forget that that triumph has all too often been tinged with tragedy. Our hospitals—the workshops which have enabled us to achieve the triumph—have also, unfortunately, been the places in which grievous harm has frequently been done to a great many people. Patients admitted for one complaint—often one that was not a threat to life, perhaps a cleft palate, a hernia, or a pregnancy—have contracted some infectious disease, and quite often have died of it. That is my rather melancholy theme.

In view of the critical reappraisal that hospital management of infectious disease cases is currently undergoing, the authors have decided to present this outbreak, despite the obsolescence of some of its preventive features, as an added contribution[3] to the scarce literature on this "melancholy theme." If the "infection control officer"—a staff member with epidemiologic qualifications—proposed by Colebrook[1] for some hospitals at least, would have been on duty in the hospital under discussion, the significance of the missed poliomyelitis case (Case 1) on the children's ward would have been recognized, and sound preventive procedures could have been promptly instituted.

Summary and Conclusions

A small outbreak of poliomyelitis, which included five paralytic cases including one of the bulbospinal type and one nonparalytic case in children aged 2-7 years, in an overseas military community is described.

The mechanism likely to have been involved in this outbreak is hypothesized, suggesting propagation by person-to-person spread and implicating a hospital in the transmission of the disease.

Medical follow-up from the time of discovery of the children exposed to a missed case of poliomyelitis on the ward could have led to the early detection of a new case, which probably has been the source of infection for three more children.

Timely administration of poliomyelitis globulin to these children could possibly have prevented or modified all or some of the subsequent cases.

The present reappraisal of the importance of infections acquired in the hospital through improper management is discussed in connection with this outbreak.

Chief, Preventive Medicine Service, Fort Jackson, S. C.

REFERENCES

1. Infections Occurring in the Hospital, Editorial, J. A. M. A. 160:290 (Jan. 28) 1956.

2. Colebrook, L.: Infection Acquired in Hospital, Lancet 2:885-890 (Oct. 29) 1955.

3. Peczenik, A., and Duttweiler, D. W.: Observations on an Outbreak of Infectious Hepatitis: Failure to Apply Accepted Control Measures, this issue, p. 101.

Case Reports

A Plethysmographic Study of the Toe of a Patient with Ainhum

GEORGE E. BURCH, M.D., and ALFRED R. HALE, Ph.D., New Orleans

Although many papers have been published on ainhum, none has been found that included plethysmographic studies of an involved toe. The present report concerns a patient at the Charity Hospital with advanced ainhum of the left fifth toe. The plethysmogram of this patient was compatible with a relatively high rate of blood flow despite pronounced pedunculation proximally, a feature confirmed by detailed histologic study following surgical removal.

The Disease

Ainhum, a term derived from an African word meaning "to saw," was first described by Clarke,[1] in 1860, before the Epidemiological Association of London. DaSilva Lima [2] recognized this disease in the Western Hemisphere in 1867. Since then, over 200 cases have been reported up to 1944, about 45 of which were from the United States.[3] There have been many isolated reports, a number from Louisiana described in 1888 [4] and 1889,[5] as well as from other parts of this country.

The disease has been variously called ayun (Yorubus), sukha, pakla (Hindu), guijila or quigila (a clinical state found with leprosy and confused with ainhum), gafeira (Portuguese), and fadiditi (Island of Nossi-Be, near Madagascar).[6] Initially, it was considered to be peculiar to the Negro, but it has since been described occasionally in peoples of other races, including Russians, Indians, and Chinese.

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From the Department of Medicine, Tulane University School of Medicine and Charity Hospital of Louisiana.

Etiology

Opinions concerning the etiology of this disease have varied considerably and have influenced many of its names. Dactylolysis spontanea has been considered an appropriate term because of the tendency for the digit to become amputated spontaneously.

Among the etiologic factors that have been considered are (1) leprosy (disproved), (2) injuries to the toes by chigoes (*Tunga penetrans*), (3) trophoneurosis, (4) localized scleroderma, (5) congenital spontaneous amputation, (6) heredity, (7) constricting fibrous tissue, (8) syphilis, (9) wearing of toe rings, and (10) infection. None of these has ever been fully established, and the early pathogenesis of ainhum still remains unknown. Patients themselves have had ideas concerning their disease; for example, a Negro woman thought she had been "hoodooed." [7]

Clinical Manifestations

The disease usually begins in a person who has had no previous difficulty with his toes. No case of congenital ainhum has been found. Patients vary in age, onset occurring in children as well as in elderly people. Involvement is usually unilateral and confined to the fifth toe but occasionally affects one of the other toes. Fingers have been said to have been involved in rare cases, but it is

not certain that this represents the same disease.

There is usually a history of trauma to the toe, produced by a farm animal stepping on the part, by carrying heavy burdens, or by injury from rocks or other objects while the patient was walking barefoot or in old shoes. The initial injury, which is usually on the plantar surface of the little toe in one of the flexion furrows, produces varied symptoms. At times, patients have had only itching of the toe, which they called "ground itch." Usually, a small papule, with or without vesicular formation and ulceration, forms in the region of initial trauma. Secondary infection is usually chronic. Subsequently, an indolent ulcer develops, associated with a putrid odor and a deepening sulcus, which marks the region of ulceration. As the disease progresses, the bone becomes absorbed, resulting in a loosely attached, pedunculated appendage distal to the sulcus that can be moved in any direction. Apparently, if the toe is not reinjured, twisted, or otherwise traumatized, it remains asymptomatic. However, carrying heavy weights, working on rough terrain, striking the toe on objects, or wearing tight shoes traumatizes the appendage and produces severe and excruciating pain. This is sometimes so excruciating that the patient will himself amputate his toe in an effort to obtain relief. At times, gangrene of the terminal portion accompanies spontaneous amputation.

Ainhum appears to be a sharply localized disease; all patients reported have been free from constitutional disturbances. A chronic, slowly progressive disease, it may last several years before amputation of the toe becomes necessary. Apparently, the rate of progress of the disease depends upon the degree of local trauma.

Unfortunately, in most instances ainhum toes have been studied clinically only when they have produced symptoms or when the patient has sought medical care. The differential diagnosis is not difficult, the characteristic sulcus and sharp localization to the toe distinguishing ainhum from Raynaud's disease, leprosy, paronychia, or any of the peripheral vascular diseases. Neurologic disturbances are easily excluded by the essentially normal sensation in the toe; it is usually warm, unless traumatized, inflamed, or gangrenous. Trauma may vary from infection to physical injury, which may cause exacerbation of the disease.

Prognosis for life has always been good. Amputation of the toe apparently results in complete relief of the patient's discomfort, with no subsequent circulatory or constitutional disturbances related to this disease. An occasional patient has had involvement of a second toe.

Pathology

In general, observers are in agreement concerning the characteristic pathologic findings of ainhum. Probably the first adequate description appeared in Duhring's report.[8] His specimen, studied by H. Wile, had become spontaneously amputated and, on external examination, revealed a "coil" of horny material wrapped around the pedicled remnant. This observation is well documented in later literature, being specifically referred to by Eyles,[9] Pusey,[10] Babler,[11] Weinstein,[12] and, more recently, by Sutton and Sutton[13] and Alldredge.[14] The observation recorded in the present report is in agreement with that of all the aforementioned investigators except Alldredge, who described this "ring" as a dense, constricting ring of connective tissue covered by a layer of epidermis.

For the most part, detailed descriptions of the microscopic anatomy of ainhum have been confined largely to the distal area of the toe. The lesion is characterized by increased thickness of the epidermis adjacent to the pedicled area, where the papillary bodies and adjacent blood vessels are elongated, dilated, and infiltrated with "round cells."[2,8,16-18] Pathologic changes deep to the epidermis of the distal toe are variously described, depending upon the degree of pedunculation. Duhring[8] described perivascular infiltration of dermal blood vessels and distention of

digital lymphatic vessels. Sweat glands were atrophic, and there was evidence of chronic inflammation. Eyles [9] described hyperplasia of dermal connective tissue, which he believed was caused by chronic inflammation, and Weinstein [12] noted increased subcutaneous tissue at the expense of the soft parts and a rarefying periosteal osteitis involving the middle phalanx. Alldredge [14] described the presence of obliterative endarteritis, whereas Sutton and Sutton [13] reported pathologic changes of smaller degree, bordering on the normal.

There seems to be much less agreement about the pathogenesis of this condition. No single study has described a graded series of specimens obtained during various phases of the disease. It has been postulated that pressure, as might be caused by a "constricting ring of dense fibrous connective tissue," produces the pedicle.[9,14,15,19] Unna [16] attributed the primary defect to annular degeneration of the skin, a sort of ring-formed scleroderma with callous formation leading to secondary stagnatory necrosis. Pusey,[10] considering the susceptibility of the Negro race to keloid formation, concluded that the pedicle is caused by a ring of fibrous tissue covered by a thickened, horny epidermis. According to Eyles,[9] the initial lesion is in the epidermis and consists in an increase in the horny layer with downgrowth of the interpapillary rete pegs.

Report of Case

A 23-year-old Negro man, admitted to Charity Hospital on March 28, 1955, had cut his left fifth toe on a piece of glass at the age of 12 years. This apparently deep laceration became infected and was treated by "old folks" remedies. The infection lasted seven to eight months and caused the young boy to limp a great deal. He was not particularly aware of his toes and feet prior to this accident but did become conscious of them after the initial injury. The patient had played football as a child and had had no difficulty with his toes. He had frequently struck the affected toe before this injury but had experienced no discomfort beyond what would be expected when any normal toe is traumatized during a football game.

After the wound healed, a short, shallow fissure was noticed on the plantar aspect of the little toe at about the region of the terminal interphalangeal articulation. The patient did not remember ever having a toenail on the involved toe. After the injury, the skin on the dorsal, medial, and lateral, as well as the plantar, surfaces of the toe had the character of plantar skin (Fig. 1). He was of the opinion that "the bottom of his toe was on the top." Over the years, a keratinous-like encrustation, with the appearance of desiccated, inspissated skin, developed in the sulcus or groove of the toe, which he routinely scraped out with a penknife. The affected toe had normal tactile and thermal sensitivity and had never been discolored or undergone any other injury than that described. No syncopal or acyanotic crises, such as are associated with Raynaud's phenomenon, had been observed.

The patient had worked in a dairy for 11 years, and about 2 years before admission he contracted "ground itch." Subsequently, the sulcus seemed to grow deeper on the medial and lateral aspects of the toe, until it finally completely encircled the toe. The patient had been unable to work at the dairy for three months before admission because the muddy, excreta-laden yard made his feet wet and cold, and moisture predisposed to continuation of his "ground itch." He therefore changed jobs and became a bricklayer's helper. On the first day of work he injured his toe walking up a flight of steps carrying a load of bricks. He experienced pain in his little toe, which initially was mild but became progressively more severe, until at the end of two days he was forced to seek medical care at the Charity Hospital.

The patient had always lived in New Orleans. His parents had previously lived on a plantation only a few miles south of New Orleans. His five brothers and two sisters were all living and well and free from any digital difficulties. One brother had frostbite during military service, but this healed uneventfully. His parents and some of his aunts and uncles who were examined were found to be free from this difficulty.

Examination of the affected toe showed it to be normally sensitive to touch. It had the same surface temperature as the other toes and seemed to have adequate circulation. The texture of the digit was similar to that of the other normal toes. There was no nail on the toe and no evidence of a specific scar or other lesion.

Laboratory data obtained on admission were within normal limits. This was consistent with

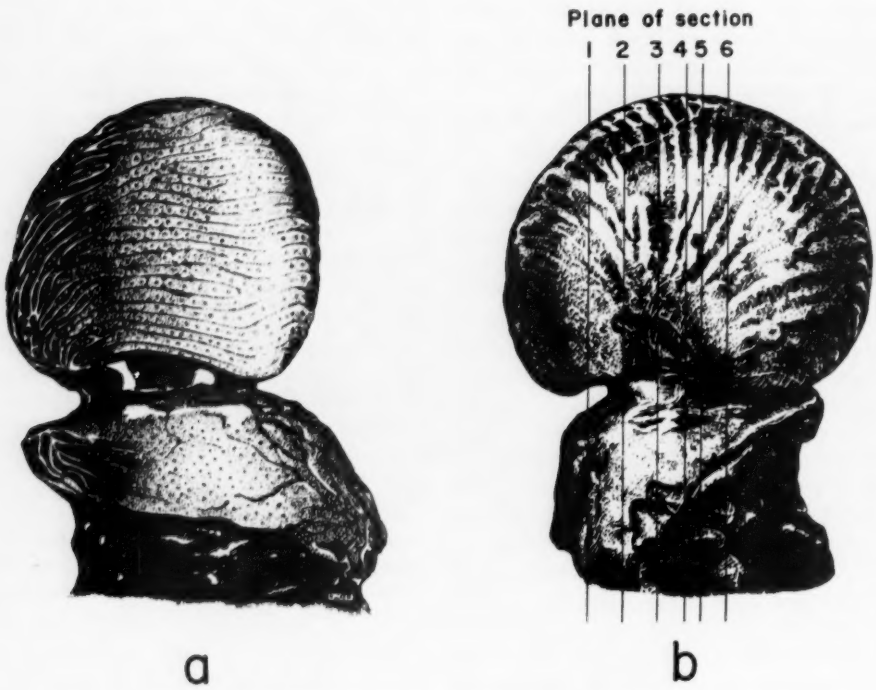

Fig. 1.—Drawing of wax replica of toe with ainhum. (*a*) Dorsal view. (*b*) Lateral view showing six levels of sections shown in Figures 6 through 8.

all cases described previously in the medical literature.

Ten days after the first admission the ainhum toe was amputated. The surgical wound healed in a normal fashion, and the patient has remained completely asymptomatic.

Plethysmographic Studies

Before the toe was amputated, plethysmographic recordings were made according to the method previously described.[20-22] A complete rheoplethysmogram could not be obtained because it was not possible to apply a venous occlusive cuff proximal to the plethysmographic

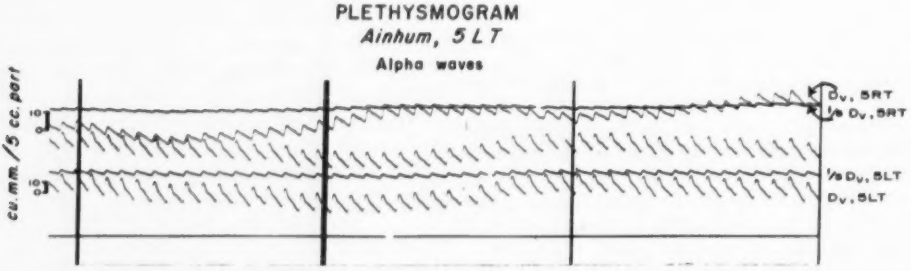

Fig. 2.—Plethysmogram of contralateral fifth right toe tip (5RT) and involved digit (5LT) of a patient with ainhum. D_V indicates volume of pulse wave. Two sets of galvanometers were used, with a sensitivity ratio of 5:1 (consult text). Unlabeled volume pulse wave should be ignored in this and all illustrations to follow.

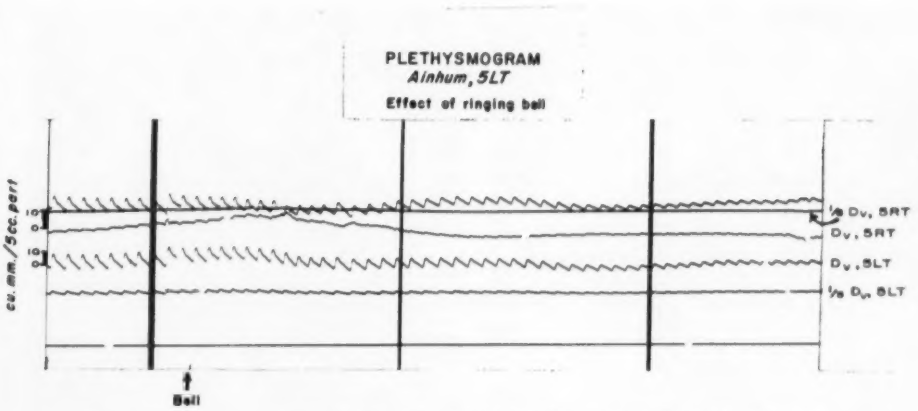

Fig. 3.—Plethysmogram showing the vasoconstricting effect of ringing a bell upon digital vessels in involved and contralateral toes of a patient with ainhum.

cup. A typical section of the plethysmogram, shown in Figure 2, reveals a volume pulse wave for the involved toe that was even greater than that for the contralateral normal toe. The pulse wave had a normal configuration and a magnitude of about 14 cu. mm/5 cc. part. Whereas the α-waves in the plethysmogram of the toe with ainhum were not as large in magnitude as those of the contralateral toe, they did seem to vary concordantly with these most of the time (Figs. 3 and 4), indicating variations in vascular tone and activity of the sympathetic innervation to the toe with ainhum.

As a test of the state of the sympathetic innervation to the vessels of that toe, a bell was rung while the subject rested alone in the observation room; constriction took place in the vessels of the contralateral side as well as in those of the involved toe (Fig. 3). Deep inspiration (Fig. 4) likewise produced constriction simultaneously in the involved toe and in the contralateral toe, a rather typical response mediated through the sympathetic nervous system.

Figure 5 shows a typical pulse wave, D_V, recorded simultaneously with the time course of the difference in the rates of inflow and outflow, D_R, and the difference in accelerations of inflow and outflow, D_A, respectively. These curves are essentially normal in configuration. D_V, D_R, and D_A curves of such magnitude are usually found in toe tips with a high rate of circulation.[21] Lastly, the plethysmograms and rheoplethysmograms of the involved toe revealed a high rate of digital blood flow, despite the rather narrow pedicle connecting the distal and proximal portions of the toe.

Morphology

Gross Examination.—Inspection of the left fifth digit, surgically removed at the base of the

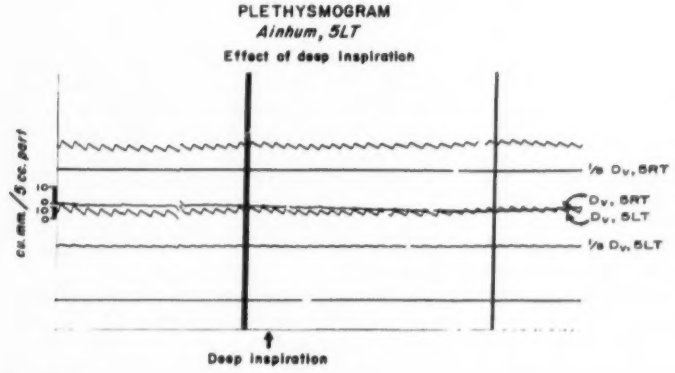

Fig. 4.—Plethysmogram showing the vasoconstricting effect of deep inspiration upon the digital vessels in the involved and contralateral toes of a patient with ainhum. The degree of vasoconstriction is reflected in the percentile change in magnitude of the volume pulse wave of 5LT.

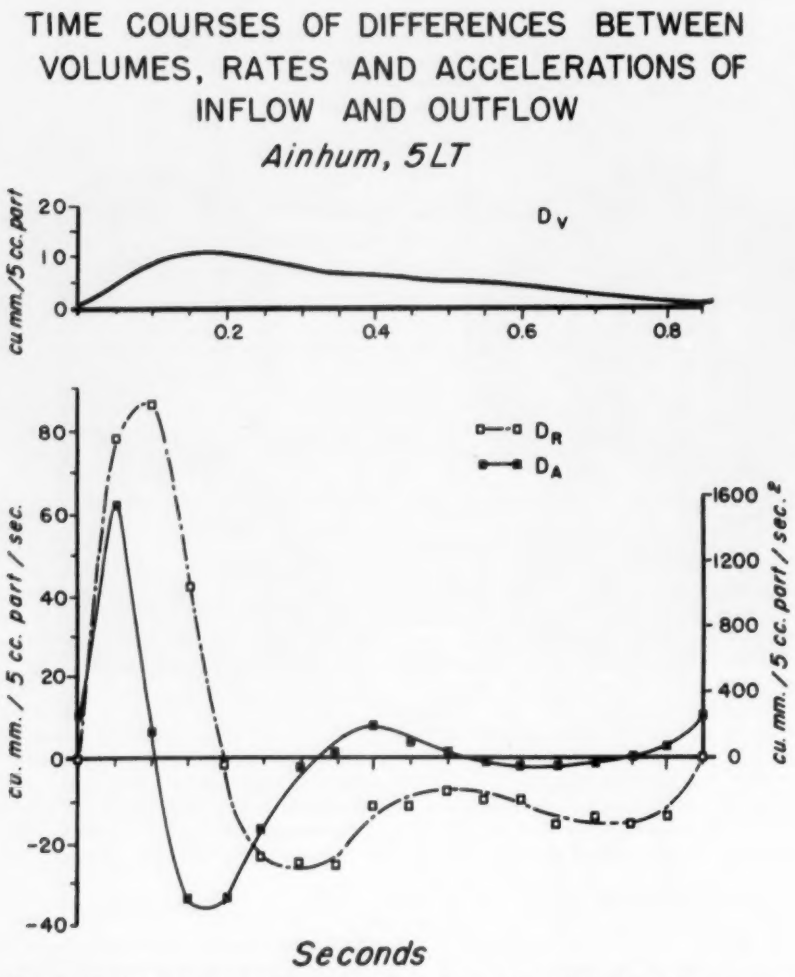

Fig. 5.—Typical pulse wave, D_V, of the involved toe of a patient with ainhum, recorded simultaneously with differences between rates of inflow and outflow, D_R, and differences between accelerations of inflow and outflow, D_A.

proximal phalanx, revealed a bulbous distal phalanx completely covered by volar skin and devoid of a toenail. The digit measured 1.8 cm. transversely, 1.7 cm. longitudinally, and 2.2 cm. vertically. Medially, where this digit was in apposition with the adjacent toe, its configuration was kidney-shaped, the smallest pole being dorsolaterally directed. An annular narrowing at the site of the proximal flexion furrow marked its connection to the foot and was filled with a cheesy, friable material, which was later completely removed as an annulus of cornified epithelial debris. Proximal to the pedicle, the skin was normal in appearance.

Examination of the subcutaneous structures beneath and above the surface of the bone proximal to the pedicle revealed the presence of two digital arteries of unequal size. The lateral digital artery was one-half the size of the medial vessel and terminated in the distal joint. The medial digital artery was traced into the pedicle and was cannulated with a No. 18 gauge needle for purposes of perfusion and injection.

Microscopic Examination.—Following cannulation of the medial digital artery, the digit was perfused with 100 ml. of isotonic saline at room temperature under 130 mm. of Hg pressure.

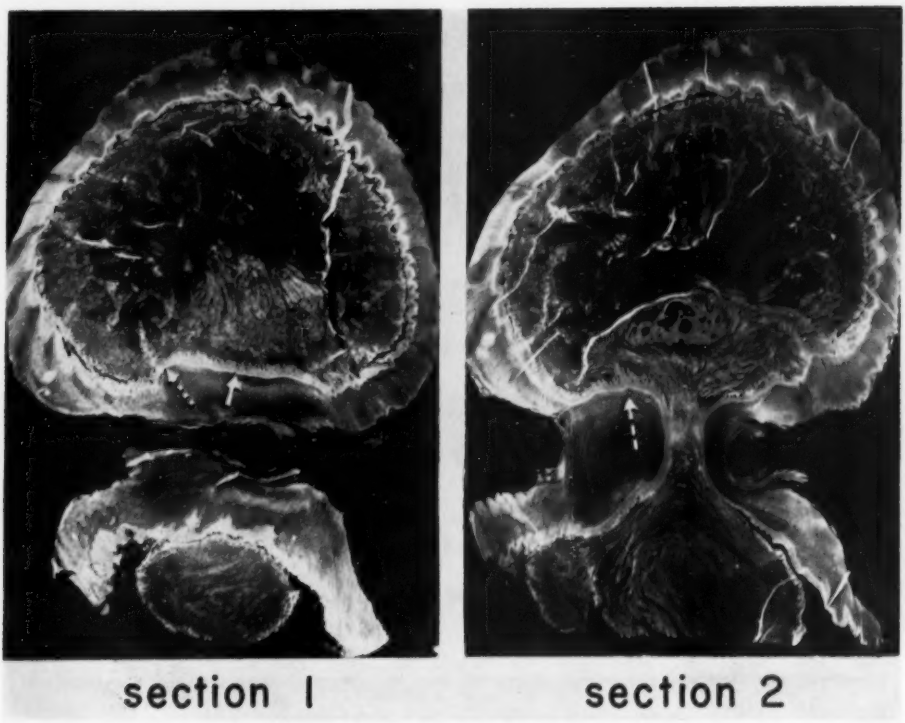

Figure 6.—Reduced approximately 1/5 from mag. × 5.

This was followed by perfusion fixation with 10% solution of neutral formalin. Decalcification was completed in four weeks with three changes of 3% nitric acid in 70% solution of ethyl alcohol.

Prior to sectioning, replicas were made of yellow wax (beeswax), paraffin, and resin mixture (7:2:1) in plasticomoulage moulds. They were exact to the smallest detail, showing the orifices of sweat glands arranged linearly on the summit of each dermal ridge. Since the specimen was without a nail or other external anatomic feature from which the plane of section could be readily identified, the wax replicas became especially useful for orientation of the histologic features of the specimen. In addition to contributing to more exact interpretation of the serial sections, they provide a permanent reproduction of the original specimen as well as a source for evaluation of dermatoglyphic peculiarities.

Routine dehydration was followed by infiltration and embedding in low-viscosity nitrocellulose according to standard methods. Serial sections 15μ to 30μ in thickness were prepared and stained with Harris hematoxylin and eosin. The first two sections passed tangentially to the dorsal surface of the specimen, resembled minute "fingerprints," and were used for the purpose of establishing the true plane of section by comparison with the surface of the wax replica.

Figure 1(*a*) was drawn from a photograph of the wax replica and illustrates the dorsal aspect of the specimen prior to sectioning. There is conspicuous absence of a nail, although, as will be pointed out in the descriptions of the individual sections, the depression on the dorsal aspect of the pedicle is considered to represent a rudimentary nail fold. The dark area at the left side of the base of the digit proximal to the pedicle represents a part of a circumferential callus to which was attached an annulus of epithelial cell debris.

The series of sections progress toward the sole of the foot in the volar plane. For purposes of description, six planes of section were selected. Their locations in the specimen are indicated by lines marked on the semidiagrammatic reconstructions of the toe shown in Figure 1(*b*).

Figure 6 (Section 1) passes above the dorsal surface of the pedicle and tangentially cuts the skin proximal to the attachment of the pedicle. The lateral aspect of the specimen is to the left of the section, the volar surface being directed downward below the surface of the plate. Examination shows the epidermis to be hyperkeratinized, especially at the distal pole of the specimen and at the areas adjacent to the edges of the proximal margin of the toe. The stratum granulosum appears as a fine white line following the festoons of volar rugae except where ridges were fortuitously cut lengthwise (see arrow).

The epidermis was separated through its lower cellular layers, leaving islands of epidermal ridges embedded in the stratum papillae of the dermis. Here, the basal cells of the epidermis showed degenerative changes, their interstices presumably being filled with a noncellular exudate. The dermal papillae appeared enlarged; their capillaries were somewhat longer, wider, and more tortuous than normal. Postcapillary venules, as well as dermal arterioles, were involved in a nonspecific perivasuclar cellular infiltration, which extended to involve the elements of subpapillary capillary plexus.

The deeper layers of the dermis appeared densely fibrous and contained an occasional dilated sweat gland duct. Arteries of the hypodermis had thickened walls but were otherwise normal morphologically. No abnormalities of the sweat glands, pacinian corpuscles, or large veins were noted at this level. Dense connective tissue extends (from the proximal dermis) into the center of the section, foreshadowing the appearance of the remains of the distal phalanx in the next section and representing, by virtue of relationship to the periosteum, what was considered to be nail bed dermis.

Attention is called to the slight lateral pocketing of the epidermis (interrupted arrow, Section 1). This area marked the beginning of an invagination that can be traced dorsolaterally to terminate in an isolated bifurcated bag of epidermis (Fig. 6, Section *2*; Fig. 7, Sections 3 and 4), which contained a lamellated mass of cornified epithelial cells.

Figure 6, Section *2*, passes tangentially through the dorsal limit of the pedicle. To the left was the abrupt indentation of the epidermis previously described (interrupted arrow, Fig. 6, Section 1). This area is of special interest, for, if properly oriented with respect to the

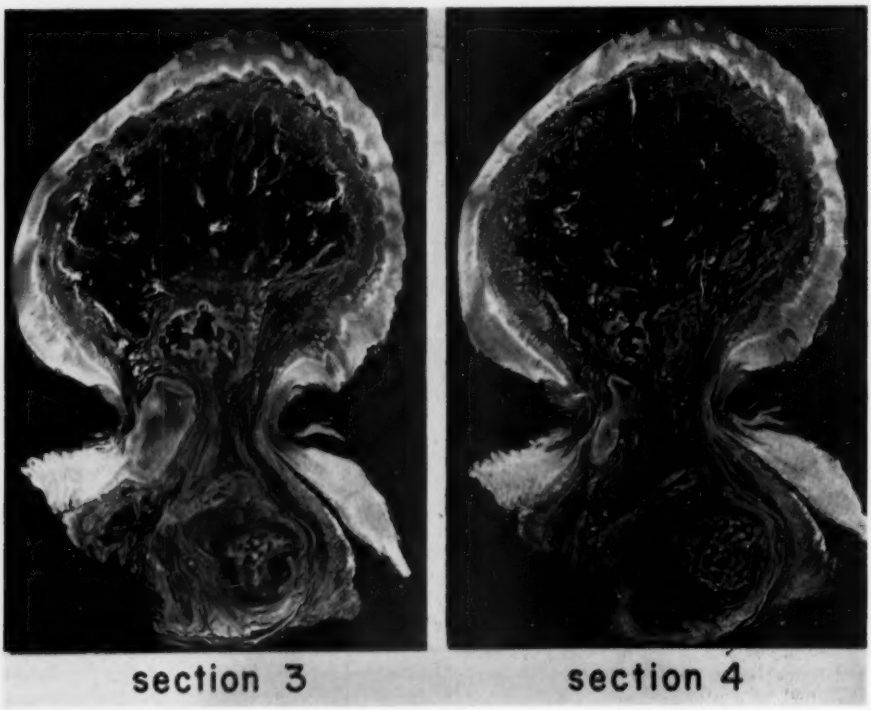

Figure 7.—Reduced approximately 3/10 from mag. ×5.

specimen as a whole (Fig. 1*a*), it is noted to occupy a position corresponding to the left margin of the nail fold.

The configuration of the epidermal ridges just dorsal to this area was characteristic of the area immediately proximal to the termination of the nail in a normally formed digit. No other area over the surface of the pedicle, by virtue of relationships or morphology, could be interpreted as being displaced nail. These observations would seem to suggest that there existed in this specimen a rudimentary nail, as represented by this specific portion of the specimen. As the skin of the pedicle is approached, the stratum malpighii and granulosum gradually disappear, and at the pedicle only an occasional basal cell could be identified.

The terminal phalanx is seen distal to the pedicle. There were only occasional areas where the cortex of the bone could be demonstrated, the bulk of the bone being composed of anastomosing trabeculae of cancellous bone, the interstices of which freely communicated with the subdermal connective tissue. The marrow elements were represented as an admixture of aggregates of fat cells and fibrous connective tissue of varying density. No myeloid marrow was identified. The periosteal blood vessels were surrounded by a nonspecific cellular infiltration characteristic of the smaller blood vessels elsewhere in the dermis. In general, there was little evidence of formation of new bone; however, aggregations of osteoclasts were linearly arranged over the irregular bone surfaces adjacent to the pedicle.

Figure 7 (Sections 3 and 4) passes tangential to the proximal phalanx through its articulation with the fragment of the middle phalanx. Comparison of the bony elements of these sections indicated that periostitis with active resorption of bone was largely confined to the fragments of the terminal and middle phalanges. The proximal phalanx appeared normal except at its articulation with the middle phalangeal fragment, at which articulation there were pannus formation and signs of inflammatory changes of the synovial blood vessels. To the left of the pedicle (Fig. 7, Section 4) can be seen the termination of the epithelial sac previously described. All cellular layers were represented except the stratum granulosum. The invagination terminates in a bifurcated cellular mass composed of elements of thickened stratum malpighii, the dermal surface of

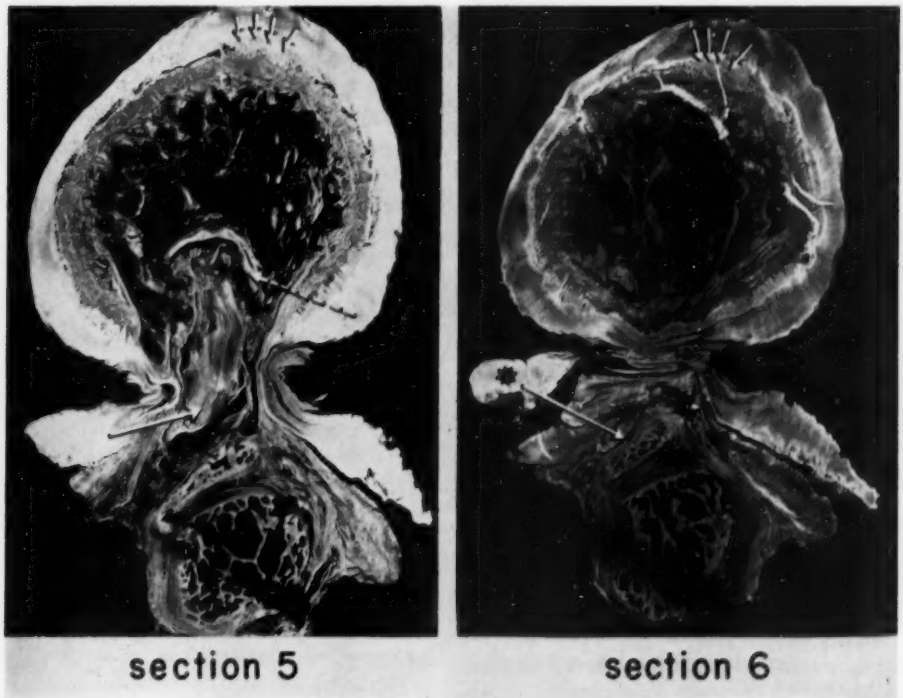

Figure 8.—Reduced approximately 1/3 from mag. × 5.

which was more or less characteristically folded in nail bed pattern. To the left, the terminal epithelial sac was covered by atrophic epidermis characteristic of skin of the pedicle. There was abrupt discontinuity of the stratum granulosum in this area, and the malpighian layer was virtually nonexistent.

The epidermis of the distal toe became extremely thickened adjacent to the pedicle. Here, the thickening involves the malpighian layer as well as the stratum corneum. The basal cell ridges and rete pegs are elongated and more anastomotic than for normal volar skin. A similar localized alteration of the thickness of the malpighian layer with changes in the morphology of the dermal surface of the epidermis could also be seen on the distal pole of the toe (Fig. 8, small arrows). Here the thickening (callus) could be traced two-thirds of the way around the digit in the sagittal plane toward the ventral surface. The circumferential "callus" at the base of the digit disappeared as the volar margin was approached. These changes in the sagittal and circumferential calluses indicated, by virtue of position, that they may have been secondary to chronic pressure arising out of abnormal digital configuration.

Throughout the entire series there was conspicuous lack of circumferentially oriented "constricting" rings of connective tissue, subcutaneous or dermal keloids, or other manifestations of the scarring process. In general, the pedicled area was characterized by a covering of an atrophic epidermis. The stratum corneum became thinned and lost its characteristic eosinophilia.

Figure 8 (Sections 5 and 6) reveals several interesting anatomic features. These sections pass proximal to the terminal phalanx and illustrate the malpositioning of the flexor tendon, which could be traced to shift laterally over the bony fragment of the middle phalanx (solid arrow, Section 5; asterisk, Section 6). At levels of Section 5 and lower, there is little connective tissue separating the flexor tendon from the atrophic skin of the pedicle. Vascular elements in the peritendineum and epitendineum appear as drawn out, collapsed endothelial tubes and, in general, are identified by the cellular inflammatory exudate surrounding their walls. The medial digital artery is illustrated in Section 5 (broken arrow), where its lumen appeared to be relatively small as compared with the walls and, if traced to lower levels, is seen to pass between the attenuated dermal elements of the skin of the pedicle and the flexor tendon laterally. The longitudinally arranged connective tissue fibers medial to this arterial vessel could be traced anteriorly, where they were seen to become confluent with the dermis of the distal toe.

Section 6 tangentially sections the inferior margin of the pedicle. The flexor tendon is seen anteriorly to come to lie immediately beneath a layer of stratum corneum, flanked on the left by an abruptly discontinuous epidermis. At this point it should be emphasized that epidermal dysplasia characteristic of the pedicled area was not abruptly demarcated. Evidence of histogenetic error can be seen to extend onto the proximal surface of the distal toe as well as the anterior margins of the skin of the first phalanx. The area of abnormal epidermis was more or less corset-shaped, the maximal narrowing as well as the most pronounced abnormality being located in the mid-pedicle.

Comment

It appears that initially, at least, there exists some peculiarity of the little toe that predisposes to the development of ainhum. Trauma, with subsequent infection and chronic inflammation, produces an advancing annular epidermal dysplasia, the position of which may involve the terminal or middle phalanx. Should the condition arise in a child and involve the structures of the nail bed, subsequent growth of the digit distal to the annulus might produce a deformity such as the specimen described in this report. The illustrations in published reports demonstrate milder degrees of external deformity of the terminal phalanx. As the pedicle narrows, desquamated epithelial cells accumulate. Continued deepening of the furrow eventually compromises the venous drainage, giving rise to an increase in intraluminal arterial pressure with subsequent thickening of the arterial walls. Local chronic inflammation extends to involve subsequently the dermal vessels adjacent to the pedicle. A resorbing periostitis, which arises in the bones, terminates in complete destruction of one or both distal phalanges. Callus formation almost always occurs at the site adjacent to the pedicle, where it seems to be the result of chronic inflammation. When a sagittal callus occurs, it is presumably due to increased chronic pressure arising out of deformity of the digit.

This particular case of ainhum was unique among those reported in the literature in three respects. Firstly, the specimen represented a more or less intermediate stage of the pathologic process and could be compared with similar and later stages previously described. Secondly, the deformity produced by the disease was of the severest magnitude, for comparison with which no complete description can be found in the literature. Thirdly, few cases of ainhum have been adequately described in which the onset occurred in a younger person.

Our patient presented many interesting features. The lesion did not appear to interfere with digital blood flow, even though the patient had been having considerable pain at the time. The plethysmographic findings were consistent with the general appearance of the toe, which was warm and sensitive to touch and had the color and texture of the uninvolved toes.

Another interesting aspect of this case was the histologic finding of an adequate number of blood vessels, which was also reflected in the plethysmogram. There were, however, histologic evidences of low-grade chronic inflammation of the blood vessels, as well as general inflammation of the tissues of the toe. Despite the presence of endarteritis and arteritis throughout the various sections of the toe, the tissues did not appear to be altered morphologically to any great extent; this observation was consistent with pathologic descriptions in the literature. The lytic process found throughout the dermis of the distal portion of the sulcus was interesting, but its cause remains unknown. This type of change has not been described previously and, therefore, may have been peculiar to this patient. The skin in the region of the sulcus was thin, with few germinal epithelial cells.

Another interesting histologic manifestation was the apparent absence of circumferentially located fibrous bands or any type of bands, even in the sulcus, that could have produced constriction or strangulation of the vessels to and from the terminal portion of the digit. From this toe, as well as from sections published from other laboratories, it does not appear that ainhum is produced by any constricting band that strangulates the circulation to the distal portion of the toe. The sections show the fibrous tissue strands to course longitudinally even in the groove or sulcus and not to course radially or circumferentially around the toe.

This patient, like all reported to date, was not born with ainhum. Various kinds of lesions simulating ainhum have been described at birth, but none of these had the same characteristic patterns on clinical, gross, and microscopic examination. The acquired lesions of ainhum do not develop at any particular age of life; they have been described in young children, adolescents, and young adults and have even been reported as appearing for the first time in old people. The age of the patient at the onset of the disease, however, may influence its clinical and pathologic features, just as age influences the clinical manifestations of hypothyroidism or hypersecretion of the pituitary growth hormone.

If ainhum is at all racial or familial in origin, it is not entirely so, for only in occasional instances has more than one member of the family had this type of lesion. If it is a genetically controlled disease, the gene must be recessive in nature. The family histories obtained so far do not support a genetic concept. A careful study of African Negroes, in whom the incidence seems to be higher, would be necessary to clarify the familial or genetic aspect of this disease. Such a study would be of considerable interest even though the disease, itself, does not seem to be of great importance as a medical or economic entity in America today.

The almost consistent localization of the lesion to the fifth toe has not been explained, nor is it known why trauma to the small toe in the region described tends to predispose to the development of such a fissure. Local tissue growth or proliferative fault may be the cause. The reason for absorp-

tion of the bone is also obscure, but, apparently, it is not due to any pronounced constriction or pressure about the blood vessels that would produce strangulation and interference with blood supply. Definite inflammation of the blood vessels and definite arteritis, with chronic inflammation in the digital tissues generally, existed in our patient, although no broken areas were found. Whether or not a chronic infection, with or without secondary fungous infection, assists in the development of this lesion is not known.

This condition may represent a local antigen reaction, but, again, this has not been investigated. The pedicle is much like that which develops about a small papilloma on the skin. It seems to be due not to any constricting band but merely to a developmental growth or repair difficulty, or both, that may or may not be related to chronic infection. Trauma, such as twisting of the toe or striking it, apparently has resulted in acute disturbances of blood supply, severe pain, and spontaneous amputation from gangrene. This may be consequent to the development of thrombosis in the veins and arteries, which produces the gangrene. Carrying an extremely heavy weight when the toe is deformed may predispose to this type of trauma, with the development of the type of gangrene that occurs in the pedicle of a leiomyoma of the uterus or papilloma of the skin when it becomes twisted or strangulated. There is no definite evidence to support this conjecture, but a study of the literature would seem to suggest it. It would appear that trauma, with secondary impairment of the circulation, results in this excruciating pain.

The etiologic role of trauma and of infection, whether of fungous, low-virulence streptococcic, or staphylococcic origin, or even "ground itch" caused by migrating larvae of hookworm, is consistent with the fact that ainhum has been found only in people of low economic and social levels who work hard physically, live or work in the field, and tend to have ill-fitting, old shoes or none at all.

Summary

A typical case of ainhum in an American Negro has been described. Plethysmographic studies of the digital circulation in the involved toe revealed adequate blood supply. Detailed serial histologic sections of the amputated toe failed to show a constricting circumferential band of connective tissue but did reveal chronic inflammation of the digital arteries, periosteum, skin, and soft tissues, with much atrophy of the distal phalanx. A brief review of ainhum has been presented, with a discussion of the possible etiologic mechanism of the entity.

Tulane University School of Medicine, 1430 Tulane Ave. (12).

REFERENCES

1. Clarke, cited by Blum.[6]
2. DaSilva Lima, cited by Blum.[6]
3. Martens, V., and Norris, R. F.: Pathologic Findings in a Case of Ainhum, U. S. Nav. M. Bull. 45:745-751, 1945.
4. Day, R. H.: "Ainhum," with Case and Remarks, M. News 53:348, 1888.
5. Martin, E. D.: Ainhum, New Orleans M. & S. J. 16:603, 1889.
6. Blum, H. N.: Ainhum: Report of Case, M. Rec. 66:651, 1904.
7. Bass, J. M.: Ainhum with a Report of a Case, Nashville J. M. & S. 84:201, 1898.
8. Duhring, L. A.: A Case of Ainhum, Am. J. M. Sc. 87:150-154, 1884.
9. Eyles, C. H.: The Histology of Ainhum, Lancet 2:576-578, 1886.
10. Pusey, W. A.: The Principles and Practice of Dermatology, New York, D. Appleton & Co., 1907.
11. Babler, E. A.: Ainhum, with a Report of a Case, Ann. Surg. 48:110-114, 1908.
12. Weinstein, H.: A Description of Ainhum as Seen on the Canal Zone, with Report of Interesting Cases Occurring in One Family, South. Med. J. 6:651-656, 1913.
13. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1935, p. 624.
14. Alldredge, R. H.: Ainhum (Dactylolysis Spontanea) a Case Report with Roentgenologic and Pathologic Findings, J. M. A. Alabama 6:137-141, 1936.
15. Darling, cited by Weinstein.[12]
16. Unna, P. G.: The Histopathology of the Diseases of the Skin, New York, The Macmillan Company, 1896, p. 1114.

17. Schuppel, F. J., cited by Weinstein.[12]

18. Eyles, C. H., cited by Weinstein.[12]

19. Castellani, A., and Chalmers, A. J.: Manual of Tropical Medicine, New York, William Wood & Co., 1910, p. 1148.

20. Burch, G. E.: A Method for Recording and a Study of the Venous Occlusive Technic for Measuring the Time Course of the Rate of Inflow and the Time Course of the Rate of Outflow in the Finger Tip of Man During a Single Pulse Cycle, in a Ciba Foundation Symposium: Peripheral Circulation in Man, edited by G. E. Wolstenholme and J. S. Freeman, London, J. & A. Churchill, Ltd. 1954, pp. 23-44.

21. Burch, G. E.: Digital Plethysmography, New York, Grune & Stratton, Inc., 1954.

22. Burch, G. E.: The George E. Brown Memorial Lecture: Digital Rheoplethysmography, Circulation 13:641-654, 1956.

Aneurysms of Two Aortic Sinuses

Associated with Aortic Insufficiency, Perforation into the Left Ventricle, and Complete Heart Block with Prolonged Ventricular Arrest

FREDERICK H. KAHN, M.D.; MORTON LEE PEARCE, M.D., and E. RAYMOND BORUN, M.D., Los Angeles

The occurrence of aneurysms of two aortic sinuses, either congenital or acquired, is rare; involvement of a single sinus, although reported with increasing frequency in recent years, remains an uncommon defect. Heart block is routinely cited in textbooks of cardiology as a possible complication of right aortic sinus aneurysms because of their proximity to the atrioventricular node or the bundle of His, yet only two instances of coexisting complete heart block and aortic sinus aneurysms are reported.[1,2] Aortic insufficiency as a complication of single or multiple aortic sinus aneurysms is almost universal, being attributed to weakening and dilatation of the aortic ring by aneurysmal erosion.[3]

Complete heart block in this case was complicated by periods of ventricular asystole which soon became refractory to the usual modes of therapy, necessitating continual use of the electrical pacemaker for 15 days. Peculiar to the case to be reported here was a small perforation between the right aortic sinus aneurysm and the left ventricular chamber, which contributed in small measure to aortic insufficiency.

Report of Case

A 48-year-old actively employed Negro laborer was hospitalized on July 8, 1955, with the chief complaint of brief syncope followed by severe dyspnea several hours prior to entry. He had had known valvular heart disease since January, 1954, when he first sought medical care (V. A. Hospital, Oakland, Calif.) for symptoms of increasing exertional dyspnea since 1952. He was found to have signs of congestive heart failure and aortic insufficiency. Laboratory tests at this time were unrevealing, including negative blood and spinal fluid tests for syphilis. His symptoms of failure responded to digitalization. He resumed active employment and remained symptom-free until June, 1955, when moderate exertional dyspnea occurred. There was a past history of syphilis treated "adequately" in 1930 and again in 1954, this time with 9,000,000 units procaine penicillin.

Physical examination revealed a severely dyspneic and orthopneic man. He was afebrile. The blood pressure was 140/30 in both arms. The pulse was 40 per minute and regular. The respirations were 28 per minute. Other pertinent findings were as follows: The jugular veins were distended to the jaw. Moist rales were audible at both lung bases. The apex impulse was in the sixth intercostal space at the anterior axillary line. There was a diffuse systolic heave of the precordium, with systolic and diastolic thrills along the left sternal border; M_1 was quiet, P_2 loud, and A_2 inaudible. A very loud, rough, to-and-fro murmur was best heard at the third intercostal space, left sternal border, but was loudly transmitted over the precordium and into the neck vessels. No gallop rhythm was heard. No abdominal organs were palpable, and there was no peripheral edema. There were no dermatological or neurological stigmata of syphilis.

The blood cell count was normal. Urine examinations were normal except for slight proteinuria on admission. Serological tests for syphilis were negative. The antistreptolysin titer, mucoproteins, and C-reactive protein were within normal limits. Serum creatinine was 1.1 mg. per 100 cc.

Roentgenogram of chest revealed gigantic cardiomegaly with left ventricular preponderance. Chest fluoroscopy revealed a prominent and vigorously pulsating aortic arch. Films of the sacroiliac joints and extremities were normal.

Electrocardiogram.—Left ventricular hypertrophy, incomplete right bundle-branch block, and complete heart block at the time of admission.

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From the Veterans Administration Center and the Department of Medicine of the University of California Medical Center.

The impression on admission was aortic insufficiency of unknown cause with severe myocardial insufficiency and complete heart block, possibly due to digitalis intoxication. The cause of syncope was uncertain.

Course.—Digitalis was discontinued. Normal sinus rhythm occurred 12 hours thereafter. However, moderate heart failure, unresponsive to diuretics, persisted. On July 10, ten hours after a single dose of gitalin (0.5 mg.), complete heart block recurred with a slow idioventricular rhythm interrupted by frequent runs of rapid ventricular tachycardia associated with typical Adams-Stokes syncope. Infusions of KCl and large doses of atropine did not affect either arrhythmia, which spontaneously reverted to sinus rhythm with first degree atrioventricular block 18 hours later. Symptoms of heart failure responded to rest, diuretics, and low-salt diet. Gitalin therapy, 0.5 mg. per day, was begun on July 31. The patient returned home on Aug. 4, 1955.

On Aug. 13 he was readmitted because of increasing dyspnea and transient feelings of faintness associated with irregular palpitations. There were no signs of heart failure on physical examination. The electrocardiogram demonstrated normal sinus rhythm. Gitalin was discontinued. On Aug. 15 the patient experienced acute dyspnea and orthopnea. The pulse was 36 per minute. The electrocardiogram revealed complete heart block. Signs of heart failure returned. On Aug. 16 there were frequent bouts of ventricular arrest with syncope, unresponsive to sublingual and intramuscular isoproterenol, ephedrine, and large doses of atropine. Epinephrine prevented ventricular arrest, but on Aug. 17 no medication was effective. The patient was now in severe heart failure. The electrical pacemaker,[4] heretofore used periodically, was now operated constantly to induce a heart rate of 70, and after several hours a profound diuresis occurred (amounting to 540 cc. in the first 6 hours and 3185 cc. in 30 hours) and was associated with some improvement of his heart failure. From Aug. 17 to Aug. 31 frequent attempts were made to induce spontaneous ventricular rhythm by drastic means. One-third and one molar sodium lactate infusions[5] induced idioventricular rhythm only when supplemented by epinephrine and always increased the patient's symptoms of heart failure. Interestingly, while he received sodium lactate, light rhythmic manual pounding over the precordium induced ventricular complexes and peripheral pulses coincident with the blows to the chest. Infusions of epinephrine and isoproterenol caused a transient idioventricular rhythm. However, anuria developed at the infusion rate of epinephrine (0.009 mg. per minute) necessary to induce ventricular systole. From Aug. 17 to Aug. 31 there was progressive deterioration. Heart failure increased in spite of redigitalization and various diuretic measures. On Sept. 1, with the artificial pacemaker in constant operation, a Hufnagel valve[6] was inserted without difficulty.*

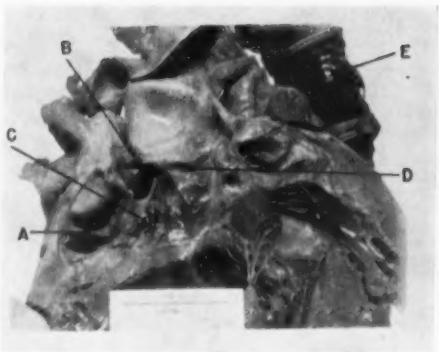

Fig. 1.—View of the aortic valve and aorta. *A*, septum dividing the left sinus aneurysm. *B*, orifice of the right sinus aneurysm. *C*, site of perforation between the right sinus aneurysm and the left ventricle. *D*, posterior (noncoronary) semilunar valve. *E*, Hufnagel valve.

Autopsy.—Other than the changes of acute and chronic passive congestion of the viscera and the presence of a bifid left ureter, significant findings at postmortem examination were limited to cardiac and aortic abnormalities. The heart weighed 840 gm.; the foramen ovale and ductus arteriosus were closed. There was tremendous hypertrophy of the left ventricle, and there was moderate hypertrophy of the right. The valves, other than the aortic, were normal. The circumference of the aortic ring was 14 cm. The posterior semilunar valve and its commissures and the edges of the left and right semilunar valve immediately adjacent to the posterior valve were normal. The remainder of the left and right cusps were thickened and depressed, accounting for an estimated 16 sq. mm. area of aortic incompetency. The commissure between the abnormal cusps was slightly separated.

Right Aortic Sinus Aneurysm: Extending from the edge of the right semilunar cusp to the junction of the membranous and muscular interventricular septum was a roughly cuboidal pouch with a volume of 16 cc. A low thick septum between the interventricular septum and the valve cusp divided the pouch into an anterior and a posterior chamber. Two ancillary pockets in the floor of the anterior chamber projected into the lumen of the

* Performed by Drs. F. X. Byron and J. Fields. Eight hours postoperatively spontaneous idioventricular rhythm ensued at a rate of 70. Signs of heart failure diminished. The patient died on Sept. 3, 1955, when a sudden prolonged ventricular asystole did not respond to electrical stimulation.

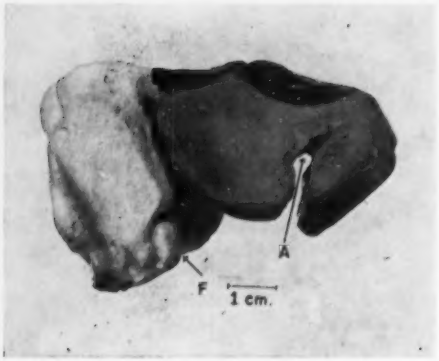

Fig. 2.—Plastic (acrylic) imprint of the left (dark) and right (light) sinus aneurysms. View of the interventricular surfaces of the aneurysms. The left aneurysm lies adjacent to the right ventricular outflow tract and two cusps (black) of the pulmonary artery. *A*, space occupied by septum of the left sinus aneurysm. *F*, space occupied by the septum of the right sinus aneurysm.

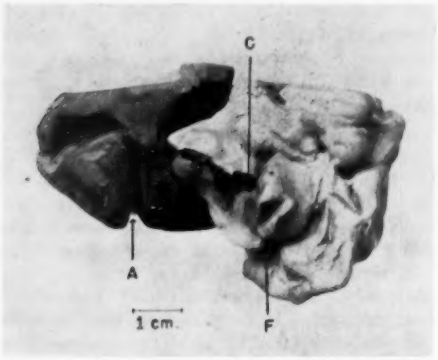

Fig. 2B.—Plastic (acrylic) imprint of the left (dark) and right (light) sinus aneurysms. View of the aneurysms from the lumen of the left ventricle. *A*, space occupied by the septum of the left sinus aneurysm. *C*, site of perforation between the right sinus aneurysm and the left ventricle. *F*, space occupied by the septum of the right sinus aneurysm.

left ventricle. One of these pockets communicated with the left ventricular chamber through several small perforations.

Left Aortic Sinus Aneurysm: This aneurysm qualitatively resembled the right aneurysm in general appearance and in depth, but it measured only 12 cc. It also was divided into two pouches by a thick-walled septum, higher than that on the right, which united near the nodulus of the left semilunar valve, the union resembling an aberrant commissure. The left aneurysm dissected between the pulmonary artery and the anterior chamber of the right sinus aneurysm. There were no pockets or perforations of the left sinus aneurysm.

Surfaces of the aneurysms and the semilunar valves were smooth, yellow, and glistening, with

Fig. 3A.—Section of the aorta at the edge of an atheromatous plaque; reduced 1/3 from mag. × 75.

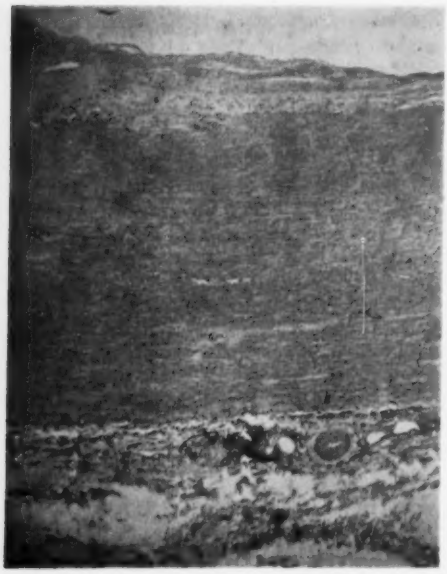

Fig. 3B.—Section of the left coronary artery; reduced 1/3 from mag. × 100.

scattered patches showing gradations to a wrinkled brown. The aorta was elastic, normally thin-walled, without dilatation; its circumference was 10 cm. Throughout its course there was a scattering of atheromatous plaques, several being wrinkled. The Hufnagel valve was well secured without leakage.

Microscopic Findings.—Aorta: Sections of the ascending and descending thoracic aorta, uninvolved by atheromata, revealed slight collagenous thickening of the adventitia which was sparsely infiltrated by round cells. Rare vasa vasorum were thickened. Adventitial vascularity was increased. A few arterioles were bounded by moderately dense collections of lymphocytes, plasma cells, and histiocytes. Adjacent to the atheromata there was patchy disruption of the elastic media associated with minimal cellularity and vascularity. Adventitial changes were similar but more prominent than those of the plaque-free areas.

Valves and Septa: The posterior semilunar valve was normal, but the right and left valves were fibrous. Centrally there was moderate vascularization and infiltration by lymphocytes, plasma cells, and histiocytes.

Coronary Arteries: There were adventitial changes resembling those of plaque-free sections of aorta.

Aortic Sinus Aneurysms: Large areas of the walls were involved by recent subendocardial infarction. Areas not infarcted showed changes similar to those of the atheromatous aorta.

Clinical Observations

In this patient the coexistence of serious aortic insufficiency and complete heart block with a slow ventricular rate resulted in refractory heart failure. On his first admission, heart block was complicated by Adams-Stokes syncope due to paroxysms of ventricular tachycardia; normal sinus rhythm appeared when digitalis was discontinued. On his final hospitalization the occurrence of heart block was associated with increasingly prolonged bouts of ventricular standstill necessitating continual stimulation by the electrical pacemaker.[4] With an artificially induced heart rate of 70 per minute there was a tremendous diuresis and amelioration of heart failure. Heart failure and oliguria recurred during periods of spontaneous slow idioventricular rhythm. Special studies of this patient, published elsewhere,[7] graphically demonstrated the close relation of heart rate and renal function. A minimal heart rate of 70 per minute was essential for maintenance of cardiac compensation and renal blood flow; this criterion alone made it obvious that the standard pharmacological remedies used in heart block would be ineffective in this patient. The agents employed in this case included sublingual isoproterenol, atropine and ephedrine injections, and intravenous epinephrine and isoproterenol. The latter two drugs caused very brief elevations of the ventricular rate. One-third and one molar sodium lactate infusions[5] neither prevented ventricular asystole nor significantly increased the heart rate; however, lactate infusions definitely augmented the effect of epinephrine injections. In this patient lactate therapy precipitated pulmonary edema and had the additional disadvantage of causing extensive local phlebitis. On the basis of a report of the successful treatment of refractory heart block with steroids,[8] our patient received cortisone in large doses over a two-week period with no change of his arrhythmia.

The progressive physical and mental deterioration during the 15 days of continual application of the electrical pacemaker and the failure of a practical medical regimen influenced the decision to attempt surgical treatment. It was hoped that inserting a Hufnagel valve would allow cardiac compensation even with a slow ventricular rate. It was conjectured that improved cardiac function, the result of diminished diastolic load, might terminate the ventricular standstill. Eight hours postoperatively spontaneous ventricular rhythm occurred. Borderline cardiac compensation was maintained until the terminal ventricular standstill, on the third postoperative day.

Pathological Observations

The commonly cited causes of aortic sinus aneurysms are cardiovascular syphilis, endocarditis involving a congenital or acquired valve deformity, and uncomplicated congenital malformation, thought to be the

result of failure in fusion of the proximal and distal bulbar swellings during the differentiation of the bulbus cordis into the aorta and pulmonary artery in early embryologic development. According to this postulation, congenital aneurysms can involve only the right and posterior aortic sinuses,[9] and in a majority of reported congenital aortic sinus aneurysms, this seems to be the case. However, Micks [1] described a case involving congenital aneurysms of three sinuses and cited three similar cases in the literature. Recently it was suggested that congenital aortic sinus aneurysms are the result of congenitally defective elastic tissue,[10] implying that the aneurysms develop much later embryologically. This explanation would account for uncomplicated aneurysms of the left aortic sinus.

When obvious anatomical clues, such as syphilitic aortitis, multiple cardiac malformations, or endocarditis, are absent, an etiological diagnosis tends to be a speculative matter. Such was the case in this patient; but the weight of evidence favors the diagnosis of cardiovascular syphilis. The patient's history of "adequate" chemotherapy of a primary syphilitic infection in 1930 and retreatment with penicillin 20 months before his death (although there was no serological evidence of active syphilis at this time) is apparently no guarantee of protection against cardiovascular syphilis, as was recently indicated by Barnett [11] in a report of 44 treatment failures; Barnett has observed a poor correlation of serological activity and progression of the cardiovascular syphilis. The autopsy findings presented a number of puzzling features. Assuming the aortic valve deformities to be the result of syphilis, then the relatively normal gross appearance of the ascending aorta is unusual. The histological findings in the adventitia of the aorta and coronary arteries and walls of the aneurysms are consistent with syphilitic infection, although the changes are minimal. Conceivably the disproportion of serious valve and aortic sinus deformity and minimal inflammatory alterations on microscopic examination was related to antisyphilitic therapy or possibly cortisone administration. There are only four reports [12-15] of the effects of treatment on the microscopic appearance in cardiovascular syphilis; there is fair agreement that adequate treatment is associated with a healing process in which the cellular infiltration and endarteritis is diminished. A photomicrograph representing healed syphilitic aortitis is seen in the report of Webster and Reader (Autopsy 11032),[14] closely resembling the aorta in our patient. Cortisone is said to inhibit greatly the inflammatory response to acute syphilitic infection in rabbits.[16]

Whether a valid analogy can be made to the chronic human infection is not known. It is conceivable that cortisone contributed to the paucity of histological alterations in this patient.

Unique septa divided each aneurysmal pouch. The union of the left sinus aneurysm septum with the edge of the left semilunar cusp suggested the existence of a congenital supernumerary semilunar cusp. However, applying Koletsky's histological criteria for differentiating septa of acquired and congenital bicuspid aortic valves,[17,18] the septa in this case are acquired and are assumed to be an uncommon manifestation of syphilitic aortic sinus aneurysms.

Summary

A case of aneurysms of the left and right aortic sinuses is presented. The coexistence of the aortic insufficiency and complete heart block resulted in severe refractory heart failure. During treatment of prolonged ventricular asystole by external stimulation of the heart, it was found that a pulse of over 70 per minute induced a diuresis and amelioration of heart failure. No pharmacological agent available maintained a ventricular rate sufficient to prevent heart failure. The patient's deterioration during 15 days of continual application of the electrical pacemaker influenced the decision to insert a Hufnagel valve. Postoperatively spontaneous idioventricular rhythm ensued,

and borderline cardiac compensation was maintained. During the long period of ventricular arrest the surgical procedure was the only treatment which induced a continual, spontaneous, effective ventricular rhythm.

Because of several unusual features at postmortem examination, an etiological diagnosis could not be established with certainty, although the weight of evidence favored the diagnosis of acquired aneurysms of the left and right aortic sinuses due to cardiovascular syphilis.

Dr. Ben Fishkin, of the Department of Pathology, performed the postmortem examination and helped in formulating the comments on the pathological material. Dr. Simon Koletsky, of the Department of Pathology, Western Reserve University, and Dr. William Carnes, Department of Pathology, Stanford University, reviewed the microscopic section of the aorta and aortic sinus aneurysms.

Cardiology Section, Veterans Administration Center, Wilshire & Sawtelle Blvds. (25) (Dr. Pearce).

REFERENCES

1. Micks, R. H.: Congenital Aneurysms of All Three Sinuses of Valsalva, Brit. Heart J. 2:63, 1940.

2. Duras, P. F.: Heart Block with Aneurysm of the Aortic Sinus, Brit. Heart J. 6:61, 1944.

3. Snyder, G. A. C., and Hunter, W. C.: Syphilitic Aneurysm of the Left Coronary Artery with Concurrent Aneurysm of the Sinus of Valsalva, and an Additional Case of Valsalva Aneurysm Alone, Am. J. Path. 10:757, 1934.

4. Zoll, P. M.; Linenthal, A. J., and Norman, L. R.: Treatment of Stokes-Adams Disease by External Electric Stimulation of the Heart, Circulation 9:482, 1954.

5. Bellet, S.; Wasserman, F., and Brody, J. I.: Treatment of Cardiac Arrest and Slow Ventricular Rates in Complete A-V Heart Block: Use of Molar and Half Molar Sodium Lactate; a Clinical Study, Circulation 11:685, 1955.

6. Hufnagel, C. A.; Harvey, W. P.; Rabil, P. J., and McDermott, T. F.: Surgical Correction of Aortic Insufficiency, Surgery 35:673, 1954.

7. Pearce, M. L., and Nordyke, R.: Some Observations on the Effect of Heart Rate Controlled by an External Stimulator in Aortic Insufficiency, Am. J. Med. 22:498, 1957.

8. Lown, B.; Arons, W. L.; Ganong, W. F.; Vazifdar, J. P., and Levine, S. A.: Adrenal Steroids and Auriculoventricular Conduction, Am. Heart J. 50:760, 1955.

9. Jones, A. M., and Langley, F. A.: Aortic Sinus Aneurysms, Brit. Heart J. 11:325, 1949.

10. Venning, G. R.: Aneurysms of the Sinuses of Valsalva, Am. Heart J. 42:57, 1951.

11. Barnett, C. W.: Failure of Adequate Treatment in Preventing Cardiovascular Syphilis, Stanford M. Bull. 13:234, 1955.

12. Hood, B. J., and Mohr, C. F.: Microscopic Pathological Appearance of the Aorta in Treated and Untreated Patients with Syphilitic Aortitis, Am. J. Syph. 21:177, 1937.

13. Howe, E. G.: Microscopic Pathological Appearance of the Aorta in Treated and Untreated Cases of Syphilitic Aortitis, Am. J. Syph. 27:50, 1943.

14. Webster, B., and Reader, G. G.: Effect of Antisyphilitic Treatment on the Microscopic Appearance of Syphilitic Aortitis, Am. J. Syph. 32:19, 1948.

15. Sinclaire, H. A., and Webster, B.: Effect of Penicillin Treatment on the Microscopic Appearance of Syphilitic Aortitis, Am. J. Syph. 38:54, 1954.

16. Turner, T. B., and Hollander, D. H.: Studies on the Mechanism of Action of Cortisone in Experimental Syphilis, Am. J. Syph. 38:371, 1954.

17. Koletsky, S.: Congenital Bicuspid Aortic Valves, Arch. Int. Med. 67:129, 1941.

18. Koletsky, S.: Acquired Bicuspid Aortic Valves, Arch. Int. Med. 67:157, 1941.

Periodic Paralysis Associated with Hyperthyroidism

LT. COL. E. L. OVERHOLT (MC); MAJOR VERNON M. SMITH (MC), and CAPT. E. D. WHITE (MC), U. S. Army

Periodic paralysis as described by Talbott [1] is characterized by intermittent attacks of flaccid paralysis of the muscles of the extremities with loss of deep tendon reflexes and response to electrical stimulation of the motor nerves.[2] During attacks there is an associated hypokalemia which responds to treatment with potassium salts. The paralysis usually begins peripherally with more profound involvement of the extensor muscles. It may be partial, complete, localized, or generalized. There is a normal sensorium and absence of sensory changes, and the paralysis rarely involves the muscles of deglutition and phonation or the eye. Temporary bradycardia, hypotension, dilatation of the heart, and increase in the size of the paralyzed muscles have been reported. The paralysis may be present for a few hours to two or three days, and recovery proceeds in the reverse direction to the order of onset. Approximately 80% [3] of the reported 450 [4] cases have been familial. There is a male predominance of three to one in the familial cases. In the sporadic cases it is rarely seen in the female. It usually occurs in young people under 30 and ceases in the fourth decade [5] spontaneously.

Rosenfeld [6] reported the first case associated with thyrotoxicosis in 1902, although Charcot and Mobius, cited by Dunlap,[7] earlier had reported the occurrence of paraparesis and paraplegia associated with thyrotoxicosis. Linder,[4] in an extensive review of the literature since 1902, found 35 cases with these two associated conditions and added 4 more.

Submitted for publication April 24, 1956.

Report of Case

A 27-year-old white man of Russian extraction was initially seen by one of us (V. M. S.). He was referred to the U. S. Army Hospital, Landstuhl, Germany, on Oct. 5, 1955, with the diagnosis of periodic paralysis associated with hyperthyroidism. Since June, 1955, he had experienced at least 10 episodes of profound weakness of all four extremities and occasionally of the trunk musculature. Characteristically, the episodes of weakness began between 2 a. m. and 5 a. m. and at times precluded his turning over in bed. Dressing in the morning required the aid of his wife. The weakness gradually subsided to mild weakness in the thigh by noon. Between episodes, he noted an occasional stiffness of the legs after sitting for a prolonged period. The patient described his acute attacks as a "feeling of heaviness with a dull ache in my muscles which would rapidly progress to weakness to the point where I could not control my arms, legs, or trunk." He had no respiratory distress or cranial nerve symptom. His attacks usually occurred after a "hard day of work," or after a large carbohydrate meal, such as spaghetti, the evening before. However, these were not always followed by weakness in the morning.

In response to direct questioning, he recalled having had mild heat intolerance, increased sweating, emotional lability, mild tremor of the hands and, despite a large food intake, a 10-lb. weight loss since May, 1955. There was no history of a similar disease in his family.

Physical examination revealed a slender, alert, healthy-appearing young man. The blood pressure was 130/64. The pulse was 95. The thyroid was slightly enlarged, the right lobe more than the left. There were no palpable nodules or regional adenopathy. There was a slight, fine tremor of the hands, and the skin was moist, flushed, and warm. No other abnormality was noted.

Laboratory data included a normal c. b. c., sedimentation rate, urinalysis, cardiolipin test, liver profile, blood cholesterol, and chest film. Initial serum PBI determinations were 9.6γ and 10γ per 100 cc. (normal, 3.5 to 8.0) on Oct. 7 and 8, respectively. The oral glucose tolerance test revealed a fasting blood sugar of 128 mg/100 cc.

TABLE 1.—*Record of the First Induced Attack**

Date and Status	Time	K, mEq./L.	P, Mg./100 Cc.	Muscular Involvement
Oct. 21, 1955				
Control	2 p.m.	4.4	4.3	None
Spaghetti meal	5 p.m.	--	--	None
200 gm. CHO orally, 20 units insulin, and 0.5 cc. 1:1,000 epinephrine	12 p.m.	--	--	None
Oct. 22, 1955				
Onset of attack	2 a.m.	3.2	4.2	2+
	5:15 a.m.	2.7	3.3	4+
30 mEq./L.I.V. and 4 gm. orally of KCl	6 a.m.	2.6	2.2	4+
	8 a.m.	2.6	1.99	4+
	9 a.m.	3.6	2.95	2+
	10 a.m.	4.4	3.75	1+
	11 a.m.	5.4	4.55	1+
	12 noon	5.7	4.2	None

* Muscle involvement is graded from 0 to 4+. Note the correlation o fserum potassium and phosphorus levels with muscle involvement.

and a two-hour level of 134 mg/100 cc. Blood potassium was 4.2 mEq/liter, and the inorganic phosphorus, 3.2 mg/100 cc. Twenty-four-hour urine contained a normal creatinine of 1.8 gm., creatine of 0.04 gm., coproporphyrin of 109γ, and no uroporphyrin.

During a 15-day period of observation his sleeping pulse varied between 90 and 105. On limited activity in the hospital he had no difficulty, but after going on pass, he noted a brief episode of weakness which he attributed to the increased activity. A full-blown attack of paralysis was induced in the following manner: At 5 p.m. on Oct. 21, 1955, the patient was fed a large spaghetti meal. At 12 p.m. he was given 200 gm. of carbohydrate orally, 20 units of insulin subcutaneously, and 0.5 cc. of 1:1000 epinephrine subcutaneously. By 2 a.m. Oct. 22, 1955, the patient complained of moderate weakness which rapidly progressed, so that by 5 a.m., he was unable to sit up, turn over, lift his leg, or move his arms except the fingers. Detailed tests for muscle involvement were performed to compare the degree of severity with subsequent attacks and to evaluate potassium therapy. There was marked weakness of the infra- and supraspinatus, deltoid, biceps, triceps, and brachioradialis muscles; mild weakness of the extensors and flexors of the hands, and mild weakness of the abductors and, adductors of both hands. There was marked weakness of the hip flexors and extensors, moderate weakness of the quadriceps and hamstring muscles, and marked weakness of the peroneus muscles and extensor hallucis longus. The weakness throughout the left leg and arm was similar in distribution but not as severe as that on the right. Deep tendon reflexes were depressed throughout, and there was no evidence of sensory nerve, cranial nerve, or intercostal muscle involvement. All subsequent attacks were similar in character and varied only in severity. This attack, by gross muscle testing and by the patient's subjective evaluation, was considered his most severe episode while in the hospital.

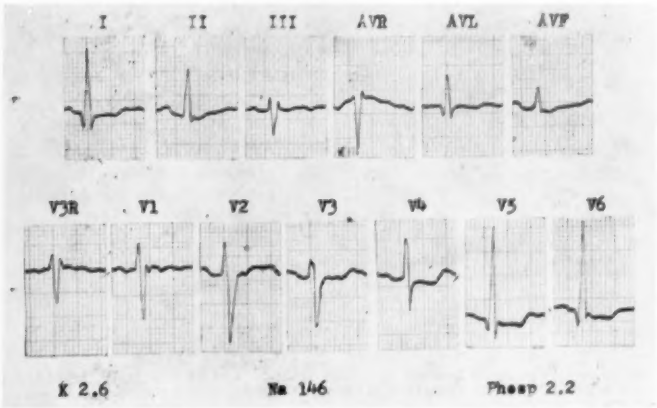

Fig. 1.—Oct. 22, 1955, 6 a.m. Typical straightening of the ST segment with apparent prolongation of the Q-T interval by a prominent U wave and diphasic to inverted T waves.

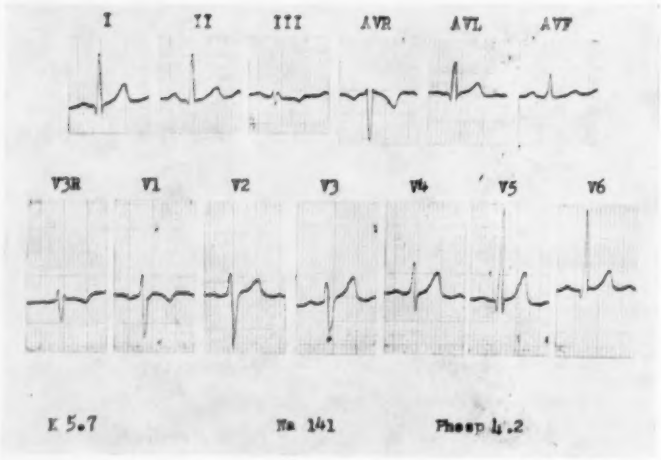

Fig. 2.—Oct. 22, 1955, 12 noon. Normal ECG with return of potassium and phosphorus to normal serum levels.

At 6 a. m. he was given 30 mEq. (2.25 gm.) of potassium chloride intravenously over a two-hour period. He also received a total of 62 mEq. (4.50 gm.) of potassium chloride orally during this same time. At 8:30 a. m. there was no significant improvement in his muscle strength. However, by 10 a. m. the patient had shown definite improvement, and by 12 noon there was complete return of all muscle function. Table 1 reflects the correlation of the potassium and phosphorus with clinical course and response to therapy. Typical changes of hypokalemia were demonstrated by the electrocardiogram (Figs. 1 and 2). On the evening of Oct. 26, 1955, a milder attack was precipitated under similar circumstances (Table 2 and Fig. 3). Potassium therapy was withheld during this episode to ascertain, by comparison with the more severe attack induced earlier, whether potassium administration actually shortened the attack. The muscular weakness, reflex changes, and blood potassium and phosphorus abnormalities did not return to normal until 8 p. m.

Frequent checks of the blood pressure and pulse during this episode revealed no significant changes. Administration of 0.5 mg. of neostigmine (Prostigmin) intravenously had no effect on muscle function. Muscle response to faradic and galvanic stimulation was subnormal. Measurements of the arm, forearm, calf, and thigh muscles revealed no change in size. A tourniquet applied to the right arm with a blood pressure cuff at the diastolic blood pressure level for 45 minutes produced no improvement in the function of the right arm.

On Nov. 1, 1955, the patient experienced a spontaneous attack of moderate severity, again accompanied by typical blood chemistry and electrocardiographic changes. Forty-seven milli-

TABLE 2.—*Record of the Second Induced Attack**

Date and Status	Time	Glucose, Mg./100 Cc.	K, mEq./L.	Na, mEq./L.	Ca, Mg./100 Cc.	P, Mg./100 Cc.	CO_2 Vol.%	Muscular Involvement
Oct. 26, 1955 Spaghetti meal	5 p.m.							None
200 gm. CHO orally, 20 units insulin, and 0.5 cc. 1:1,000 epinephrine	12 p.m.							None
Oct. 27, 1955	12:15 a.m.	154	3.4	133.0	9.9	4.70	67.2	1+
	1:15 a.m.	--	2.8	130.0	--	4.70	--	2+
	2:20 a.m.	--	2.9	132.5	10.0	4.70	--	2+
	3:20 a.m.	--	3.1	132.5	9.0	4.70	--	3+
	5:15 a.m.	--	3.0	130.0	--	4.50	65.0	3+
	6:45 a.m.	120	2.7	130.0	9.8	3.00	--	3+
	8:15 a.m.	--	2.6	130.0	--	2.35	--	3+
	10:15 a.m.	--	2.6	135.0	--	2.60	--	3+
	12:15 p.m.	--	3.0	135.0	--	3.60	62.0	2+
	2:15 p.m.	132	3.3	135.0	--	4.05	--	2+
	5:15 p.m.	--	3.8	135.0	--	4.60	--	1+
	8:30 p.m.	--	5.2	135.0	--	4.10	--	None

* Correlation of serum potassium and phosphorus to muscle involvement again is evident. Low levels of potassium and phosphorus and muscle involvement persisted much longer due to withholding of potassium therapy. There was no correlation with the blood glucose, serum sodium, serum calcium, or CO_2.

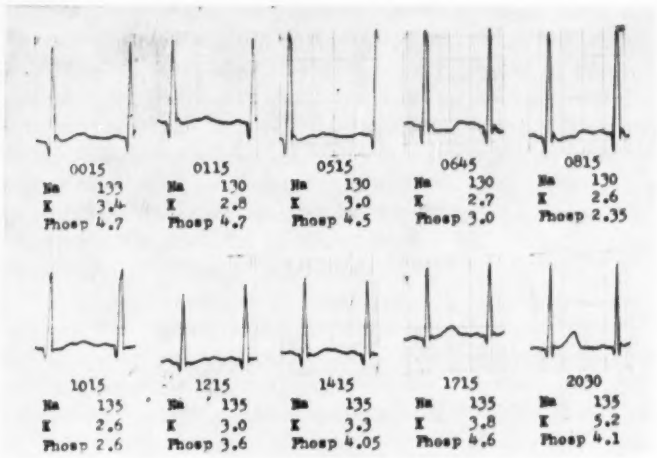

Fig. 3.—Serial leads of V_6, Oct. 27, 1955. Note the progressive changes with the altered potassium and phosphorus levels. Initially there is lowering of the amplitude of the T wave and appearance of the U wave. The ST segment becomes straightened and the T wave isoelectric as the serum potassium decreases. What appears to be a diphasic T wave is actually a U wave at the end of the isoelectric T wave, and the Q-T interval is actually the Q-U interval. Note also the increase in the R wave with the hypokalemia.

equivalents (3.5 gm.) of potassium chloride orally every hour was associated with return of muscle function to normal within four hours. Throughout this period of investigation he had been on a regular hospital diet with no added potassium. After this last episode, the patient was placed on a low carbohydrate diet with 120 mEq. (9.0 gm.) of supplemental oral potassium chloride daily. No spontaneous attack occurred while on this diet. Methimazole (Tapazole), 10 mg. t. i. d., was begun on Oct. 28, 1955, and continued through Nov. 23, 1955. Potassium iodide, 5 drops t. i. d., was given from Nov. 16 through Nov. 28, 1955. By Nov. 15 the sleeping pulse had fallen to 82 and the patient had gained 10 lb. in weight and clinically appeared to be approaching adequate thyroid control. In addition, his serum PBI had fallen to 6.0γ per 100 cc. The low carbohydrate diet and added potassium chloride was discontinued to ascertain whether he would have any spontaneous episodes while euthyroid. Three days later he had an attack of paresis in the early morning hours. The low-carbohydrate-high-potassium diet was resumed, and he had no further difficulty. On Nov. 28 a subtotal thyroidectomy was performed without event. The thyroid was hyperplastic and revealed partial involution. Attempts to induce episodes in the manner previously utilized were unsuccessful three weeks following surgery and at a three-month postoperative reevaluation. At this time the potassium, phosphorus, PBI, fasting blood sugar, and glucose-tolerance curve were normal. There were no symptoms or signs of hyperthyroidism, and there had been no spontaneous attacks of muscle weakness.

Comment

It is apparent that cases of periodic paralysis may be divided into three general groups. Commonly, they occur without apparent associated systemic disease in several members of certain families. A sporadic form is associated with hyperthyroidism. A third group of cases do not appear to be either familial or related to another systemic disease. Attacks of the paralysis may be induced in susceptible persons by physostigmine, pilocarpine, parathyroid parathormone, posterior pituitary (Pituitrin), acetylcholine,[1] prolonged use of corticotropin (ACTH), testosterone, insulin, epinephrine, desoxycorticosterone, ingestion of large amounts of carbohydrates, and water diuresis.[1,8,9] Shinosaki[10] showed that periodic paralysis associated with thyrotoxicosis is aggravated by thyroid administration, and Dunlap[7] noted recurrence of paralytic attacks when his treated cases of thyrotoxicosis relapsed.

During an attack the phosphate may fall[11] along with a decrease in the potassium. However, there is a decrease in the urinary potassium and phosphorus, indicating a probable internal shift of ions.[1,11,12] It has been shown that phosphate, potassium, and glucose tend to transport together to and from the blood. Insulin, epinephrine, or ingested glucose increase liver content of potassium and phosphorus. It has been shown that deficiency of potassium at the neuromuscular junction results in paralysis

of the muscle. It is postulated that in persons with periodic paralysis there is an increased demand for potassium in glycogenesis and glycogenolysis due to some unknown defect in the muscle cell and that not enough potassium is left to resynthesize the high-energy phosphate system, resulting in muscle weakness or paralysis.[13,14] McQuarrie [15] has shown that a diet in which the ratio of carbohydrate to potassium is higher than 75 to 1 causes attacks of paralysis. This concept would be readily acceptable if all cases showed definite changes in the amount of available potassium or respond to adequate potassium therapy. However, certain contradictory observations have been made. Tyler,[16] Seed,[17] and Hildebrand [18] did not observe dramatic improvement in the patients after giving potassium. Tyler, in 1951, reported no fall in serum potassium in 33 cases of periodic paralysis during spontaneous and induced attacks.[16] Low serum potassium in such conditions as diabetic coma treated with insulin, Addison's disease treated with desoxycorticosterone, chronic nephritis, and severe acute diarrhea have been unaccompanied by muscle paralysis of the severe type found in periodic paralysis.[11,17,19,20] Considerable investigation has been done in an attempt to explain these discrepancies, but as yet there has been no complete explanation which applies to every case. This led Hofmann [21] to conclude that the symptoms of periodic paralysis merely represent the "final common pathway for widespread metabolic disorder and that it should be considered a symptom complex rather than a clearly defined disease entity."

In reference to our case, the attacks of paralysis were similar to those previously described in the literature. The improvement in muscle strength and deep tendon reflexes was slow but definite after potassium therapy in the first induced attack. The second episode clearly demonstrated that withholding potassium prolonged the period of muscular weakness and the low serum levels of potassium and phosphorus. Definite lowering of serum potassium and phosphorus was demonstrated in every attack, and there was a good correlation of their level with electrocardiographic changes and with the status of the muscle and reflex changes. No cardiac arrythmia, cardiac enlargement, muscular enlargement, or significant correlation to the blood glucose, sodium, calcium, or CO_2 was noted. Primary aldosteronism was ruled out by the absence of hypertension, hypernatremia, polyuria, polydipsia, and hyposthenuria. The electrocardiographic changes were typical of hypokalemia. They demonstrated, in the earlier stage, flattening of the T wave and a prominent U wave. As the degree of hypokalemia increased, the RST segment became depressed and the T wave became inverted or dyphasic. Interestingly, the height of the R wave increased. Most authors state that the Q-T interval is prolonged because of the broadened T wave. Lepeschkin, cited by Fenn,[23] however, believes that the Q-T is actually decreased and ascribes the apparent prolongation to the U wave, which may be mistaken for the dyphasic or notched T wave. A Wenckebach phenomenon has also been described.[4,21]

The attacks of periodic paralysis in this case were clearly related to the carbohydrate metabolism. It was shown that high carbohydrate intake, with or without insulin and epinephrine, induced attacks. Furthermore, after the patient was placed on a low-carbohydrate-high-potassium diet, no further spontaneous attack occurred. However, when the patient approached the euthyroid state, the special diet was discontinued, and he promptly had an attack of paralysis three days later. The low-carbohydrate-high-potassium diet was reinstituted with no further episode. The spontaneous remission following the return to a regular diet, although the serum PBI was normal and the hyperthyroid state was approaching normal, deserves further clarification. Our goal was to suppress adequately the hyperthyroidism to permit early surgery. More prolonged medical therapy or subtotal thy-

roidectomy would be necessary to return the patient to a completely euthyroid state. It is very likely that there was still some excessive thyroid hormone effect present, prompting spontaneous exacerbation when the low-carbohydrate-high-potassium diet was discontinued. If this were true, one may postulate a relatively high sensitivity to the thyroid hormone in this condition. Three months following surgery the fasting blood sugar and glucose-tolerance curve were normal, and it was no longer possible to induce attacks.

It is not completely clear how thyrotoxicosis and periodic paralysis may be related. Since thyroxine tends to mobilize glucose from glycogen [14] and potassium shifts from the cells with the sugar,[23] one would not expect a low serum potassium and paralysis as a direct consequence of the endocrine disorder. Pedersen et al.[24] examined the serum levels of potassium preoperatively and postoperatively in 15 cases of hyperthyroidism without finding abnormal values. Hildebrand and Kepler [18] felt that hyperthyroidism brings out a latent tendency towards periodic paralysis in the affected persons. Many patients with familial periodic paralysis also have a palpable thyroid without showing obvious signs of hyperactivity of the gland.[21] There is a rather high incidence of goiter in these families as well. In our case the patient was not aware of the mild symptoms of hyperthyroidism until they were elicited on detailed questioning. The picture may be further confused by the profound anxiety that often attends the episodes of paralysis. The fact that periodic paralysis usually comes on after puberty and tends to regress with age and decrease during pregnancy suggests to some a primary endocrine disorder.[25] One cannot help but speculate as to whether many of the cases previously described might not have had mild hyperthyroidism which would be detectable by our more refined tests such as a serum PBI determination or I^{131} uptake. It is well to emphasize that this disease is not entirely benign, for several fatalities have been reported. Every case should be thoroughly evaluated for thyroid overactivity, since all of the reported cases have shown prompt disappearance of the attacks of paralysis with the cure of hyperthyroidism.[4]

Summary

As case of periodic paralysis with associated hyperthyroidism is presented, and the literature is briefly reviewed.

Attacks were induced by a high carbohydrate intake, insulin, and epinephrine, and were prevented by a low-carbohydrate-high-potassium diet.

There was good correlation of the degree of muscle involvement and electrocardiographic changes with serum levels of potassium and phosphate. Potassium therapy definitely shortened the attacks.

Spontaneous episodes of paralysis did not occur, nor was it possible to provoke an attack following thyroidectomy. Hyperthyroidism should be ruled out in each case of periodic paralysis.

Medical Service, 2nd General Hospital, APO 180, New York.

REFERENCES

1. Talbott, J. H.: Periodic Paralysis: Clinical Syndrome, Medicine 20:85-143 (Feb.) 1941.

2. Mitchell, J. K.: Case of Family Periodic Paralysis, Am. J. M. Sc. 118:513-527 (Nov.) 1899.

3. Herrington, M. S.: Successful Treatment of 2 Cases of Familial Periodic Paralysis with Potassium Citrate, J. A. M. A. 108:1339 (April 17) 1937.

4. Linder, M. A.: Periodic Paralysis Associated with Hyperthyroidism: Report of 3 Cases, Ann. Int. Med. 43:241-254 (Aug.) 1955.

5. Bickerstaff, E.: Periodic Paralysis, J. Neurol. Neurosurg. & Psychiat. 16:178-183 (Aug.) 1953.

6. Rosenfeld, M.: Acute aufsteigende Lähmung bei Morbus Basedow, Berlin Klin. Wchnschr. 39:538-540 (June 9) 1902.

7. Dunlap, H. F.: Syndrome Resembling Familial Periodic Paralysis Occurring in the Course of Exophthalmic Goiter, Endocrinology 15:541-546 (Nov.-Dec.) 1931.

8. ACTH: Pamphlet, Chicago, The Armour Laboratories, July, 1950.

9. Gammon, G. D.: Relation of Potassium to Family Periodic Paralysis, Proc. Soc. Exper. Biol. & Med. 38:922-924 (June) 1938.

10. Shinosaki, T.: Klinische Studien über die periodische Extremitätenlähmung, Ztschr. ges. Neurol. u. Psychiat. 100:564-611 1926.

11. Allott, E. H.: Observations on Familial Periodic Paralysis, Clin. Sc. 3:229-239 (April) 1938.

12. Gammon, G. D.; Austin, J. H.; Blithe, M. D., and Reid, C. G.: The Relation of Potassium to Periodic Family Paralysis, Am. J. M. Sc. 197:326-332 (March) 1939.

13. Gass, H.; Cherkasky, M., and Savitsky, N.: Potassium and Periodic Paralysis: Metabolic Study and Physiological Considerations, Medicine 27:105-137 (Feb.) 1948.

14. Danowski, T. S.; Elkinton, J. R.; Burrows, B. A., and Winkler, A. W.: Exchange of Sodium and Potassium in Familial Periodic Paralysis, J. Clin. Invest. 27:65-73 (Jan.) 1945.

15. McQuarrie, I.: The Clinical Significance of Hypopotassemia, presented at Annual Clinical Conference, Chicago Medical Society, March, 1947, pp. 91-95.

16. Tyler, F. H.; Stephens, F. E.; Gunn, F. D., and Perkoff, G. T.: Studies in Disorders of the Muscle: Clinical Manifestations and Inheritance of Type of Periodic Paralysis Without Hypopotassemia, J. Clin. Invest. 30:492-502 (May) 1951.

17. Seed, L.: Periodic Paralysis in a Patient with Exophthalmic Goiter Controlled by 6-Propylthiouracil, West. J. Surg. 55:640-646 (Dec.) 1947.

18. Hildebrand, A., and Kepler, E.: Familial Periodic Paralysis Associated with Exophthalmic Goiter, J. Nerv. & Ment. Dis. 94:713-721 (Dec.) 1941.

19. Holler, J. W.: Potassium Deficiency Occurring During Treatment of Diabetic Acidosis, J. A. M. A. 131:1186-1189 (Aug. 10) 1946.

20. Castleden, L. I.: Effect of Adrenalin on Serum Potassium Level in Man, Clin. Sc. 3:241-245 (April) 1938.

21. Hofmann, W. W.: The Syndrome of Periodic Paralysis, Neurology 2:1-14 (Jan.-Feb.) 1952.

22. Surawicz, B., and Lepeschkin, E.: The Electrocardiographic Pattern of Hypopotassemia With and Without Hypocalcemia, Circulation 8: 801-828 (Dec.) 1953.

23. Fenn, W. O.: The Deposition of Potassium and Phosphate with Glycogen in Rat Livers, J. Biol. Chem. 128:297-307 (April) 1939.

24. Pedersen, S.; Maddock, W. G., and Winslow, S.: Serum Potassium in Hyperthyroidism, J. Lab. & Clin. Med. 23:1123-1127 (Aug.) 1938.

25. Wolf, A.: The Effective Use of Thyroid in Periodic Paralysis, New York J. Med. 43:1951-1963 (Oct. 15) 1943.

Central Nervous System Sarcoidosis Successfully Treated with Prednisone

D. P. FITZPATRICK, M.D., and G. E. EWART, M.D., Richmond, Va.

Sarcoidosis is defined as a chronic indolent and benign disease of unknown cause involving skin, lymph nodes, eyes, salivary glands, lungs, and bones of the hands and feet.[1] It is also well known that sarcoidosis can involve practically every organ system of the body, including the central nervous system.[2,3] The incidence of nervous system involvement in this disease is estimated between 1% and 5%, with lesions commoner in peripheral and cranial nerves than in the central nervous system.[2,4,5] Colliver, Hook, and Meyer et al. discuss the problem of nervous system sarcoidosis but do not report any cases treated with steroid hormones.[2,4,6] Pennell reported two cases of central nervous system sarcoidosis treated with corticotropin (ACTH) and cortisone without beneficial effect.[7] Olsen, on the other hand, discussed a case of sarcoidosis with Bell's palsy and spinal fluid changes treated with corticotropin and streptomycin with rapid recovery.[8] On review of the literature, we were unable to find any cases of central nervous system sarcoidosis favorably treated with steroids. However, it is becoming more evident that steroid therapy has a place in the management of sarcoidosis, especially in those cases in which vital structures are involved or hypercalcemia and renal insufficiency occur.[9-13] It is the purpose of this paper to report a case of sarcoidosis with marked involvement of the central nervous system successfully treated with prednisone.

Report of Case

A 32-year-old Negro man was admitted to an outside hospital on March 25, 1955, in a comatose state. Available history was poor, but the patient was said to have developed personality changes, lethargy, drowsiness, and frequent headaches over the past three or four years. He was seen by his family physician, who described a rapid change to a semicomatose state with a right hemiplegia over a period of 24 hours. Physical examination on admission revealed a young Negro man in a comatose state, unresponsive to commands, but responding to painful stimuli. The blood pressure was 120/75; pulse rate, 84, and temperature, 98.6 F. The eyes were deviated to the left. The corneal reflex was absent on the right. There was suggestive blurring of the optic disks, rigidity of the neck on flexion, and flaccid paralysis of the right side of the face and the right upper and lower extremities. The Hoffmann and Babinski signs were negative bilaterally, and the deep tendon reflexes were increased on the right. Spinal fluid studies showed a pleocytosis with lymphocytes predominating, marked increase in protein, decreased sugar, and an increased spinal fluid pressure of 220 mm. of water. Subsequent lumbar punctures were essentially unchanged, except that the spinal fluid pressure was within normal limits. Complement fixation tests were negative for lymphocytic choriomeningitis, eastern and western equine encephalomyelitis, St. Louis encephalitis, psittacosis, and lymphogranuloma venereum. Heterophile agglutinations were negative. Hemogram and cardiolipin were normal. Urinalysis was normal except for 2+ albuminuria. Cultures of the spinal fluid were consistently negative for tubercle bacilli, fungi, and bacteria. Total serum proteins were consistently elevated, with an increase in the globulin fraction. Cultures of the sputum and the blood were also negative. Chest film showed an abnormal density in the region of the right pulmonary artery and slight ventricular enlargement. Repeat films were unchanged except that the heart was thought to be smaller. Two electrocardiograms showed depressed S-T segments and T wave inversion in V_1 through V_6 and inverted T waves in aV_F but a subsequent electrocardiogram was interpreted as within normal limits.

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From the Medical Service, Veterans' Administration Hospital.

The patient was thought to have tuberculous meningitis and treated for five months with isoniazid, streptomycin, and aminosalicylic acid. The patient ran a febrile course for three weeks, but after this time he slowly improved, as evidenced by clearing of his mental status and hemiplegia. However, despite five months of antituberculous treatment, the patient became markedly worse. He complained bitterly of headache and became irritable and agitated, slept excessively, and had episodes of fever. He was then transferred to the Veterans Administration Hospital, Richmond, Va., with the tentative diagnosis of space-occupying lesion of the brain.

On admission to the Veterans Administration Hospital, the patient was found to be agitated, combative, and oriented to person only. The blood pressure was 124/80; the pulse, 108, and the temperature, 101.4 F orally. He was observed to walk with a wide base. The fundi were negative. Motor strength and coordination appeared normal. Sensation could not be evaluated. The Hoffmann and Babinski signs were negative. There were palpable cervical lymph nodes. The liver and spleen were not palpable. Eunuchoid features, female distribution of hair, and atrophic testes were noted.

Laboratory studies revealed a total protein of 8.4 gm., with 3.9 gm. of albumin and 4.5 gm. of globulin. White blood cell count was 4250, with 46% neutrophils, 37% lymphocytes, 7% monocytes, and 10% eosinophils. Several total protein determinations and white blood cell counts were essentially unchanged. Hemoglobin was 13 gm., sedimentation rate was 31. Blood urea nitrogen was 9 mg. per 100 cc., and serum calcium was 9.6 mg. per 100 cc. Protein-bound iodine was 3.7γ per 100 cc. Total cholesterol was 278 mg. per 100 cc. Cultures of the spinal fluid were negative for acid-fast bacilli and fungi. Spinal fluid pressure was 140 mm. of water, with normal dynamics. The fluid was clear. Total protein of the spinal fluid was 300 mg. per 100 cc., the sugar was 51 mg. per 100 cc., and chlorides were 121 mEq/liter. Twenty-nine cells were counted, with twenty-six lymphocytes and three neutrophils. Repeat skin tests with first- and second-strength tuberculin were negative. Chest film revealed a marked increase in size of the right paratracheal and bilateral hilar nodes.

In view of the abnormal chest film, dysproteinemia, eosinophilia, persistently abnormal spinal fluid changes, and negative skin tests, a scalene node biopsy was done. The histologic diagnosis was lymph node granuloma, consistent with sarcoidosis. The patient's clinical course became progressively worse. He was observed to sleep excessively, to complain bitterly of headache, and to be agitated when aroused. He ran an intermittent febrile course. Isoniazid and streptomycin were continued prophylactically. Because of the downhill course of the patient, he was given prednisone in initial doses of 80 mg. daily, which was reduced to 40 mg. in two days and then to 20 mg. as a maintenance dose. Four days after initiation of steroids, he complained less of headache, was less agitated, and became afebrile. After 10 days of therapy, he was no longer considered a nursing problem. Chest films taken 7 and 12 weeks later showed a definite decrease in the size of the right paratracheal and bilateral hilar masses.

Because of the marked clinical and x-ray improvement, the prednisone was discontinued after three months of treatment. Shortly thereafter, the patient became febrile, slept for long intervals of time, and again complained of headache. Prednisone was resumed after two weeks, resulting in marked clinical improvement.

During the follow-up period of nine months, the patient has remained well. He has been continued on maintenance prednisone. Follow-up chest films have shown further regression of the paratracheal and hilar masses. Hemogram, urinalysis, and total proteins are all normal. Spinal fluid findings studied in August, 1956, have improved. Spinal fluid pressure was 140 mm. of water, and no cells were seen. The fluid was clear. Total protein determination was 76 mg. per 100 cc.; the sugar, 58 mg. per 100 cc., and the chlorides, 118 mEq/liter.

Comment

It seems reasonable to assume that the clinical findings in this case are consistent with sarcoidosis primarily involving the central nervous system. This is said because of the clinical picture of headaches, somnolence, confusion, agitation, and hemiplegia. Abnormal spinal fluid findings were present and consisted of increased spinal fluid pressure, persisting spinal fluid pleocytosis, increased spinal fluid proteins, and decreased spinal fluid sugar. These, in the presence of negative skin tests for tuberculosis; many negative spinal fluid cultures for acid-fast bacilli, fungi, and bacteria; normal complement fixation studies for viral diseases of the central nervous system; negative studies for tumor and tuberculosis, and

the positive findings of abnormal hilar-paratracheal densities and biopsy showing a granulomatous lymph node consistent with sarcoid, make central nervous system sarcoidosis the most likely diagnosis.

The beneficial effect of prednisone in this case is noteworthy and clear. The patient underwent a prompt remission clinically. Serial chest films showed a progressive decrease in the size of the paratracheal and hilar masses. Laboratory findings also improved as evidenced by a return of elevated globulin fraction of the serum to normal and a loss of eosinophilia. One of the most remarkable results of treatment was the improvement in the spinal fluid.

It is interesting to note that the patient relapsed when prednisone was withdrawn. It is not likely that this was due to a rebound phenomenon, as the drug was discontinued for two weeks. During this time the patient did not improve but became clinically worse, with fever, excessive drowsiness, and severe headaches. The occurrence of an exacerbation of the disease when the drug was discontinued and the improvement noted when prednisone therapy was resumed is deemed further evidence that prednisone exerted a favorable effect on this man's illness and evidence against a spontaneous remission of sarcoidosis. The patient's clinical well-being coupled with measurable improvement in chest films, laboratory tests, and spinal fiuid while on maintenance therapy of prednisone is additional evidence that sarcoidosis with central nervous system involvement is benefited by steroid therapy.

It is our feeling that patients with sarcoidosis treated with steroid hormones should also be given antituberculous chemotherapy. This is done because of the occasional development of tuberculosis in patients with sarcoidosis and the well-established, harmful effect of prolonged steroid hormone therapy in patients with tuberculosis. However, in patients with sarcoidosis involving vital structures, it seems that the need for steroid therapy far outweighs the danger of tuberculosis developing during treatment.

Therefore, it is concluded that these patients should be treated with steroids if their disease is progressing or if their clinical condition is serious. To wait for spontaneous remission to occur in the face of a seriously ill patient with central nervous system signs might well be disastrous.

It is well established that sarcoidosis is a serious disease if vital structures are involved or when hypercalcemia and renal insufficiency occur.[3,10,12,14] It is reported that sudden death may occur from sarcoid involvement of the heart or central nervous system.[3] Since steroid therapy exerts a favorable effect upon sarcoidosis and may be life-saving, the responsibilities of the physician in establishing the nature of the illness are increased. In any patient admitted or seen in coma, convulsing, or with signs of increased intracranial pressure, sarcoidosis should be considered in the differential diagnosis. Meyer et al. reported a patient who was explored neurosurgically because of rapid fatal development of increased intracranial pressure due to sarcoidosis.[6] Since the pituitary and hypothalamus are involved on occasion, central nervous system sarcoidosis should be considered as a possible cause of diabetes insipidus and hypopituitarism.[7,14] Saliant points that may lead to a diagnosis of sarcoidosis in a patient with an obscure neurological disorder are lymphadenopathy, a palpable liver or spleen, skin lesions, eye lesions, and joint deformity. An elevated serum protein determination or globulin fraction is of great importance, and a negative second-strength tuberculin test is also helpful. A chest film is often characteristic. The presence of enlarged hilar and paratracheal lymph nodes with or without pulmonary infiltrations suggests the possibility of sarcoidosis as the etiology. X-ray of the hands and feet may on occasion show lesions of sarcoidosis, especially in the presence of peripheral joint deformity without joint pain.[3] An abnormal electrocardiogram in the presence of other suspi-

cious findings of sarcoidosis may bring up the question of sarcoid involving the heart. Spinal fluid findings in central nervous system sarcoidosis are not diagnostic, but show moderate pleocytosis with lymphocytes predominating and increased proteins and chlorides, and the spinal fluid sugar may be decreased.[7] Therefore, whenever clinical findings suggest the possibility of sarcoidosis an attempt for a histologic diagnosis should be made, as institution of steroid therapy in central nervous system sarcoidosis may be life-saving and dramatic.

Summary

A case of central nervous system sarcoidosis successfully treated with prednisone is presented.

The seriousness of some manifestations of sarcoidosis and the importance of steroid treatment of these are discussed. Salient points in the diagnosis of sarcoidosis are briefly mentioned.

Veterans Administration Hospital (19).

REFERENCES

1. Middleton, W. S., in Textbook of Medicine, Ed. 8, edited by R. L. Cecil and R. F. Loeb, Philadelphia, W. B. Saunders Company, 1951, p. 457.

2. Colover, J.: Sarcoidosis with Involvement of the Nervous System, Brain 71:451-475, 1948.

3. Longcope, W. T., and Freiman, D. G.: Study of Sarcoidosis Based on Combined Investigation of 160 Cases Including 30 Autopsies from Johns Hopkins Hospital and Massachusetts General Hospital, Medicine 31:1-132, 1952.

4. Höök, O.: Sarcoidosis with Involvement of the Central Nervous System: Report of 9 Cases, A. M. A. Arch. Neurol. & Psychiat. 71:554-575, 1954.

5. Ricker, W., and Clark, M.: Sarcoidosis: A Clinicopathologic Review of 300 Cases, Including 22 Autopsies, Am. J. Clin. Path. 19: 725-749, 1949.

6. Meyer, J. S.; Foley, J. M., and Campagna-Pinto, D.: Granulomatous Angiitis of the Meninges in Sarcoidosis, A. M. A. Arch. Neurol. & Psychiat 69:587-600, 1953.

7. Pennell, W. H.: Boeck's Sarcoid with Involvement of the Central Nervous System, A. M. A. Arch. Neurol. & Psychiat. 66:728-737, 1951.

8. Olsen, S.: Primær pulmonal sarcoidose med facialisparese og spinalvædzkeforandringer, Nord. med. 52:987-989, 1954.

9. Siltzbach, L. E.: Effects of Cortisone in Sarcoidosis: A Study of 13 Patients, Am. J. Med. 12:139-160, 1952.

10. Berger, K. W., and Relman, A. S.: Renal Impairment Due to Sarcoid Infiltration of the Kidney: Report of Case Proved by Renal Biopsies Before and After Treatment with Cortisone, New England J. Med. 252:44-49, 1955.

11. Lovelock, F. J., and Stone, D. J.: The Therapy of Sarcoidosis, Am. J. Med. 15:477-483, 1953.

12. Shulman, L. E.; Schoenrich, E. H., and Harvey, A. M.: Effects of Adrenocorticotropic Hormone (ACTH) and Cortisone on Sarcoidosis, Bull. Johns Hopkins Hosp. 91:371-415, 1952.

13. Phillips, R. W., and Fitzpatrick, D. P.: Steroid Therapy of Hypercalcemia and Renal Insufficiency in Sarcoidosis, New England J. Med. 254:1216-1222, 1956.

14. Gjersøe, A., and Kjerulf-Jensen, K.: Hypothalamic Lesion Caused by Boeck's Sarcoid, J. Clin. Endocrinol. 10:1602-1608, 1950.

Diabetes Insipidus Following Head Injury

HOWARD H. HIATT, M.D., and SAMUEL LOWIS, M.D., Boston

The paradox of hyperosmolarity of the extracellular fluid and reduced urinary excretion of sodium and chloride is frequently encountered in persons who have suffered head trauma. We have recently successfully treated this complication with posterior pituitary extract in a patient who had sustained a severe head injury. Evidence is presented to suggest that the electrolyte disturbance was the result of the development of diabetes insipidus. Diabetes insipidus resulting in hypernatremia in a patient with brain damage was first discussed by Peters.[1]

Report of Case

A 39-year-old comatose male painter was transferred to the Beth Israel Hospital from the Hale Hospital, Haverhill, Mass., on Jan. 28, 1956. Eight days previously he had fallen 14 ft. from a scaffolding and struck the right frontal portion of his skull on a concrete surface. He had been unconscious from the time of the fall. Examination at the Hale Hospital had revealed bleeding from both ears, marked chemosis of both conjunctivae, dilated and fixed pupils, flaccidity, and areflexia. A tracheotomy had been carried out to insure adequacy of his airway, and constant urethral drainage was being done. His urine output had been in excess of 1000 cc. daily, and the urine specific gravity had been as high as 1.020. He had been maintained on intravenous fluids and had received penicillin and intravenous sulfadiazine along with sodium bicarbonate daily.

Physical examination revealed a well-developed, well-nourished comatose man with Cheyne-Stokes respirations. Blood pressure was 150/90; temperature, 102 F; pulse, 120. There was a contusion over the right frontal area, with marked soft-tissue swelling, crepitus, and fragmentation of the right ascending process of the maxilla and nasal bones. There was dried blood in both ears with a slow flow of clear fluid from the left. There were massive right and left orbital hemorrhages. The right eye was proptosed downward and outward. The conjunctiva ballooned through the palpebral fissure, and there was subconjunctival hemorrhage. The pupils were dilated and fixed. The right arm was markedly swollen from the hand to the midshaft of the humerus. There was a tracheotomy tube in place, draining blood-tinged mucopurulent secretion. There were rhonchi over both lung fields posteriorly. Cardiac and abdominal examination was not remarkable. There was no edema. There were flaccidity and areflexia, with occasional slight limb movements on painful stimuli.

On entry the hemoglobin was 13.3 gm.; the white blood cell count, 13,000, with 73% polymorphonuclear leukocytes. The urine had a specific gravity of 1.012 and contained no protein, sugar, acetone, white cells, red cells, or casts. Blood studies carried out at the Hale Hospital on the morning of the day of entry included a serum Na of 142 mEq/liter; K, 4.0; Cl, 93, and CO_2, 33. Examination by portable x-ray suggested patchy pneumonia of the right lung, thought to be due to aspiration. The patient was placed in an oxygen tent and given 500,000 units of penicillin and 0.5 gm. of streptomycin every six hours. Because of the slight alkalosis and the normal urinary function he was given 500 cc. of 5% dextrose in 0.9% NaCl solution (D/S) to supplement the 500 cc. of 5% D/S and the 1300 cc. of 5% dextrose in water (D/W) which he had received prior to transfer to the Beth Israel Hospital.

The water and salt intake, urine output, and blood and urine studies are described in the Figure and the Table. There developed shortly after entry evidence of impaired renal reabsorption of water, as indicated by comparatively large urine volumes and by hemoconcentration. Urinary excretion of sodium and chloride decreased, concomitant with a rise in the serum sodium and chloride concentrations. On his fourth hospital day the patient's serum sodium had risen to 159 mEq/liter; his Cl, to 123, and his K, to 5.1. At this time, despite the withholding of fluid for 12 hours, his urine volume exceeded 100 cc. per hour, and the specific gravity of each urine sample was no greater than 1.006. Following the administration of 0.25 cc. of vasopressin tannate in oil there occurred a fall in the urine volume to 10 cc. per hour, a rise in urinary specific gravity to 1.022, and a gradual restitution toward normal of serum electrolytes. The effects of the vaso-

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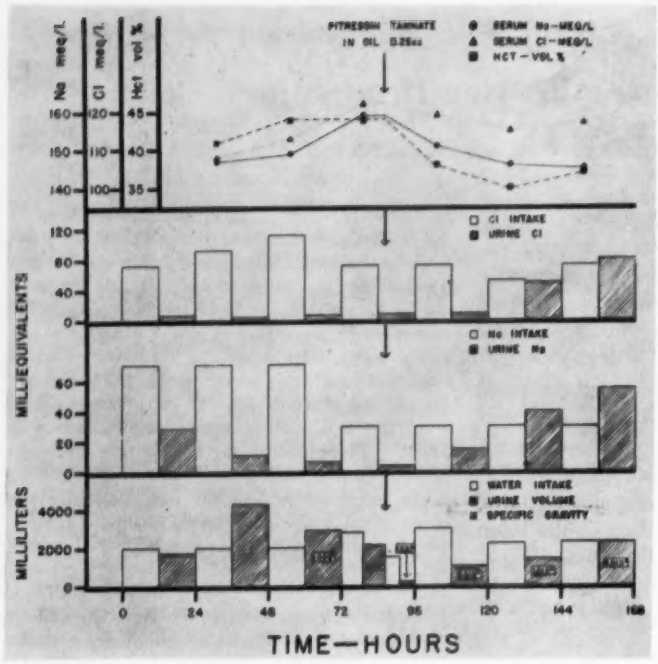
From the Departments of Medicine and Surgery, Beth Israel Hospital and Harvard Medical School.



Changes observed in comatose patient following single intramuscular injection of 0.25 cc. of vasopressin tannate in oil.

pressin were apparent for approximately 60 hours. The effect on urinary sodium and chloride excretion was marked. The urinary sodium, which had decreased steadily during the first four days of hospitalization and which was virtually absent at the time of the administration of vasopressin, gradually rose over a period of three days and thereafter approximated the sodium intake. Chloride excretion increased concomitantly. The "escape" from the effects of the vasopressin was marked by a return to relatively large urine volumes with low specific gravity, increasing hemoconcentration, and a fall in urinary sodium and chloride. However, these phenomena were never so marked as during the initial episode. On several occasions during the second week of hospitalization the administration of aqueous vasopressin intramuscularly or intravenously was followed by a fall in urine volume and a rise in specific gravity, although this response was not constant. In addition, during this period urine specific gravity as high as 1.012 was occasionally observed in the absence of therapy. Interpretation of these observations, however, is made difficult by the undoubted development of renal damage on the seventh hospital day during an eight-hour period of vascular collapse and anuria. Following this episode proteinuria was constant.

The patient's course was marked by an extension of the pneumonic process despite the administration, in order, of tetracycline and erythromycin, agents to which the invading Staphylococcus aureus had manifested in vitro sensitivity. There were frequent periods of cyanosis, and Cheyne-Stokes respiration was observed almost constantly. On the fifth hospital day temporal burr holes to explore the subdural space were made under local anesthesia. No local evidence of intracranial hematoma was found, but there was extensive fragmentation of the skull on the right and marked contusion of the surface of the brain bilaterally.

Except for the appearance of bilateral extensor-plantar reflexes and the occasional movement of extremities, the patient showed no alteration of cerebral function during hospitalization. Periods of hypotension and respiratory distress were frequent.

The patient died quietly on his 15th day in the hospital, 23 days after the occurrence of his accident. Permission for a postmortem examination could not be obtained.

Comment

Hyperosmolarity of the extracellular fluid is a more frequently reported complication in patients with head injury than is polyuria. In our subject, the rise in serum and the fall

Laboratory Data in Patient with Severe Brain Damage

Date	Intake				Urinary				Hematocrit, per Cent	N.P.N., mg./100 Cc.	Serum		
	Water, Ml.	Sodium, mEq.	Potassium, mEq.	Chloride, mEq.	Volume, Ml.	Sodium, mEq.	Potassium, mEq.	Chloride, mEq.			Sodium, mEq.	Potassium, mEq.	Chloride, mEq.
Jan. 28–29	2,000	72	0	72	1,750	27	26	9	*	*	*	*	*
29–30	2,000	72	20	90	4,250	12	51	*	44	40	147	4.2	108
30–31	2,000	72	40	112	2,850	7	151	6	44	36	149	4.6	113
31–Feb. 1†	2,800	31	40	71	2,150	8	61	6	44	41	139	5.1	123
31–Feb. 1‡	1,400	0	0	0	90	*	*	*	42.5	40	151	*	122
Feb. 1–2	3,000	31	40	71	1,010	14	75	8	38	30	151	5.0	119
2–3	2,200	31	20	51	1,400	42	232	50	35	41	146	4.2	115
3–4	2,250	30	40	70	2,240	56	36	79	37	47	145	4.0	117
4–5§	3,300	*	*	*	2,720	52	46	116	37	49	151	5.8	118
5–6	2,700	30	30	60	2,150	24	60	13	37	43	137	3.8	116
6–7	2,800	45	30	75	2,000	28	70	5	*	*	150	4.5	113
7–8	4,015	*	*	*	2,965	55	105	5	37	46	144	4.2	113
8–9	3,500	*	*	*	3,000	35	66	9	39	43	138	3.6	108
9–10	3,750	*	*	*	2,850	2	25	*	*	40	138	3.8	107
10–11	2,450	*	*	*	2,250	18	27	5	38	44	144	3.7	108
11–12	3,850	*	*	*	2,540	20	50	46	37	34	*	4.9	108

*Not measured.
†7 a.m.–11:30 p.m.; 0.25 cc. vasopressin tannate in oil I.M. at 11:30 p.m.
‡11:30 p.m.–7 a.m.
§From Feb. 4 to Feb. 13 patient received intermittent intramuscular injections of aqueous vasopressin.

in urinary sodium and chloride were far more striking than the increase in urine volume. The course of our patient, however, suggests strongly that inadequate production of antidiuretic hormone was responsible for the electrolyte abnormalities.

During the first 86 hours of hospitalization the total fluid intake was 8800 ml. His total urine volume during that period was 11,000 ml. Because he was febrile, the daily insensible water loss undoubtedly exceeded 1000 ml. Hence, the total water output during this period was at least 15,000 ml., or over 6000 ml. more than the patient received. This deficit adequately explains the rise in serum Na and Cl, particularly since the urinary excretion of these ions virtually ceased. The phenomenon of a falling urinary Na and Cl simultaneous with a rise in the extracellular concentrations of these minerals has been observed in patients with diabetes insipidus following withdrawal of hormonal therapy,[2,3] as well as in dehydration states in animals with normal pituitary function.[4] The fall in urinary electrolytes reflects the increased tubular reabsorption of Na and Cl which accompanies a contraction of extracellular fluid volume. Not until several hours after the administration of posterior pituitary hormone did urinary Na and Cl excretion rise. This delay may reflect the time required for significant water retention, which has been shown by Leaf et al. to lead to increased renal excretion of these electrolytes.[5] That our patient's 24-hour urine volume never exceeded 4200 ml. may be explained in part by what was probably a low urinary excretion of solutes. (His intake of solutes during the first week of hospitalization consisted only of 5% dextrose solutions and small amounts of sodium and potassium chloride.) It has been shown in patients with profound diabetes insipidus that urinary volumes can be markedly reduced by limitation of intake of solutes.[3] In addition, the relatively small urine volumes may have resulted from some endogenous production of antidiuretic hormone. The intermittent

finding of a urine specific gravity over 1.010 in the absence of hormone therapy during the second week of hospitalization followed an episode of prolonged and profound hypotension. Hence, while the urine concentration might have been a reflection of endogenous posterior pituitary function, the possibility exists that it was rather a manifestation of a reduced glomerular filtration rate consequent to hypotension. Both del Greco and de Wardener [6] and Berliner and Davidson [7] have recently shown that a reduced filtration rate may lead to a concentrated urine in the absence of posterior pituitary principle.[3]

While our patient's head injury was of such magnitude as to result in his death, management of his electrolyte disturbance was greatly facilitated by the administration of posterior pituitary hormone. An examination of several reports concerning serum hyperosmolarity in patients with brain damage [8-11] suggests that in at least some such patients this complication occurs as a result of derangement in posterior pituitary function and that the administration of posterior pituitary extract might prove beneficial.

Summary

A rising serum sodium and chloride, mild polyuria, a dilute urine, and very low urinary excretion of sodium and chloride were observed in a patient who had suffered a severe head injury. Improvement followed the administration of posterior pituitary hormone. It is suggested that the serum hyperosmolarity and low urinary electrolyte excretion were the result of diabetes insipidus.

Dr. Melvin Tribeman referred this patient to us, and Dr. Arnold S. Relman advised us in the management of the patient and in the preparation of this report.

Beth Israel Hospital, 330 Brookline Ave. (15).

REFERENCES

1. Peters, J. P.: The Role of Sodium in the Production of Edema, New England J. Med. 239: 353-362 (Sept. 2) 1948.

2. Engstrom, W. W., and Liebman, A.: Chronic Hyperosmolarity of the Body Fluids with a Cerebral Lesion Causing Diabetes Insipidus and Anterior Pituitary Insufficiency, Am. J. Med. 15: 180-186 (Aug.) 1953.

3. Leaf, A.; Mamby, A. R.; Rasmussen, H., and Marasco, J. P.: Some Hormonal Aspects of Water Excretion in Man, J. Clin. Invest. 31:914-927 (Oct.) 1952.

4. Elkinton, J. R., and Taffel, M.: Prolonged Water Deprivation in the Dog, J. Clin. Invest. 21:787-794 (Nov.) 1942.

5. Leaf, A.; Bartter, F. C.; Santos, R. F., and Wrong, O.: Evidence in Man That Urinary Electrolyte Loss Induced by Pitressin Is a Function of Water Retention, J. Clin. Invest. 32:868-878 (Sept.) 1953.

6. del Greco, F., and de Wardener, H. E.: The Effect on Urine Osmolarity of a Transient Reduction in Glomerular Filtration Rate and Solute Output During a "Water" Diuresis, J. Physiol. 131: 307-316 (Feb.) 1956.

7. Berliner, R. W., and Davidson, D. G.: Production of Hypertonic Urine in the Absence of Pituitary Antidiuretic Hormone, J. Clin. Invest. 35:690 (June) 1956.

8. Allott, E. N.: Sodium and Chlorine Retention Without Renal Disease, Lancet 1:1035-1037 (May 6) 1939.

9. Higgins, G.; Lewin, W.; O'Brien, J. R. P., and Taylor, W. H.: Metabolic Disorders in Head Injury: Hyperchloræmia and Hypochloruria, Lancet 1:1295-1300 (June 16) 1951.

10. Schoolman, H. M.; Dubin, A., and Hoffman, W. S.: Clinical Syndromes Associated with Hypernatremia, A. M. A. Arch. Int. Med. 95:15-23 (Jan.) 1955.

11. Leutscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. 18:741-756 (May) 1943.

Clubbing and Hypertrophic Osteoarthropathy

Two Unusual Cases

DANIEL KAHN, M.D., West Haven, Conn.

Marie,[1] in 1890, and Bamberger,[2] in 1891, first described the syndrome that bears their name, more widely known as hypertrophic pulmonary osteoarthropathy. Since that time, medical literature has recorded divergent opinions regarding the incidence of this disorder in certain diseases and the relationship of simple digital clubbing to hypertrophic osteoarthropathy.

It is accepted that a variety of common pulmonary lesions, most notably bronchogenic carcinoma, empyema, bronchiectasis, and pulmonary abscess, as well as rarer conditions, such as carcinoma of the thymus[3] and pleural mesothelioma,[4] may be associated with the disorder. The recognition of hypertrophic osteoarthropathy becomes of great import when it is realized that it may be the earliest sign of bronchogenic carcinoma. It has been emphasized that osteoarthropathy may precede, by as much as 18 months,[5] the pulmonary symptoms of neoplasm of the lung, in contrast to the slowly developing chronic variety associated with suppurative processes. Since digital clubbing may be the first manifestation of osteoarthropathy, the possibility of bronchogenic carcinoma must be considered in its presence.

Of less universal recognition is the fact that clubbing and the periosteal proliferation of osteoarthropathy may also occur in a number of various and apparently unrelated nonpulmonary conditions. These include myelocytic leukemia,[6] subacute bacterial endocarditis,[7] myxedema,[7] carcinoma of the nasopharynx,[8] biliary cirrhosis,[9] and sprue.[10] The incidence of clubbing in cyanotic congenital heart disease has been estimated as 35%-40%.[11] Vogel et al.[5] and Pugh[12] state that the bony and synovial changes of osteoarthropathy do not occur in uncomplicated cyanotic congenital heart disease, although this remains controversial. Two cases are quoted by Ray and Fisher[13] as instances of osteoarthropathy in congenital heart disease. However, one[14] had simple clubbing without mention of bony changes and the other[7] was complicated by bacterial endocarditis. Mendlowitz[15] and Locke,[9] nevertheless, maintain that clubbing and osteoarthropathy are merely stages in the evolution of the same process and that bony changes may be found in any condition with which clubbing is associated, including congenital heart disease. Schnitker[16] recognizes the rarity of the association, although conceding two cases[2,17] which authentically illustrate the relationship.

The following cases of clubbing and osteoarthropathy are presented because of their unusual nature and because they may help to clarify some of the questions herein raised.

Report of Cases

CASE 1.—The patient, a 49-year-old white man, was referred to the West Haven Veteran's Hospital on March 7, 1956, for evaluation and treatment of "peripheral vascular disease." For six months he had noticed swelling and aching of his feet, ankles and knees, without redness, warmth, or tenderness. This discomfort was worse late in the day, after standing or walking. On direct questioning, he admitted to an unpleasant feeling of fullness in the tips of all digits, with a noticeable swelling and pink discoloration. He had mild fatigability and slightly productive cough over

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From the Medical Services of the Veterans' Administration Hospital, West Haven, Conn., and Yale University School of Medicine, New Haven, Conn.

Fig. 1 (Case 1).—Bronchogenic carcinoma, illustrating digital clubbing of the hand.

this period of time, but no fever, recent weight loss, or anorexia. Past history revealed that he smoked one to two packs of cigarettes daily for many years and had nondisabling bilateral pes cavus for 13 years.

On physical examination, positive findings were limited to the extremities. Bilateral pes cavus was present. There was marked clubbing, with erythema and increased diaphoresis, of the tips of all digits (Fig. 1). Non-tender swelling of the ankles and feet, with moderate pitting, was noted (Fig. 2). The knees and lower tibiae were tender. Examination of the lungs was not remarkable.

Complete blood cell count, urinalysis, sputum cultures, and electrocardiogram were normal. A photoroentgenogram and initial full chest film were not remarkable, and films of the extremities revealed no evidence of hypertrophic osteoarthropathy. Although bronchoscopy on two occasions revealed no endobronchial lesion, bronchial washings, as well as sputum specimens, were positive on Papanicolau smear for carcinoma cells. Repeated films of the chest in expiration, inspiration, and overexposure disclosed a density in the left hilum. Planigrams revealed an indistinct density in the left lower lobe posteriorly, behind the cardiac shadow.

Left thoracotomy and pneumonectomy were performed on April 4, 1956. A firm 7 cm. diameter mass was seen in the posterolateral basal segment of the left lower lobe extending to the diaphragmatic pleura. There was a 2 cm. diameter lesion impinging on the left lower lobe bronchus 5 cm. from its origin, with bronchial dilatation distally. Enlarged lymph nodes were observed along the bronchus leading to the hilum, extending to the carina and also adjacent to the esophagus. Pathological diagnosis was mixed epidermoid and adenocarcinoma of the lung, with epidermoid invasion of lymph nodes.

Postoperatively the patient was ambulated within four to five days and reported disappearance of the pain and swelling in the ankles, feet, and knees. The clubbing, erythema, and diaphoresis previously noted in the finger and toe tips showed a distinct decrease.

Comment.—This case illustrates, first, the protean appearance osteoarthropathy may present. Initially the arthralgia and swelling of the ankles and feet were considered due to vascular disease or rheumatoid arthritis. Among the classical features of hypertrophic osteoarthropathy are bone pain aggravated by the dependent position of the extremities; clubbing; redness, warmth, glistening, and perspiration of the skin of the affected regions; bone tenderness, and rapid disappearance of the pain and swelling after treatment.

This patient also demonstrates the importance of clubbing and osteoarthropathy as one of the earliest manifestations of bronchogenic carcinoma. Even after clinical attention was focused on the possibility of a pulmonary malignancy, the initial chest film and bronchoscopy were interpreted as negative. The diagnosis was confirmed only by the use of cytological examination and

Fig. 2 (Case 1).—Note digital clubbing of the feet and marked soft-tissue swelling of the ankles.

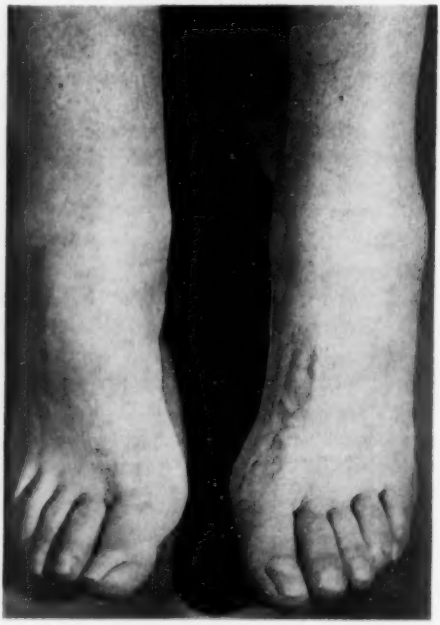

Fig. 3 (Case 2).—Eisenmenger's complex, illustrating digital clubbing of the hand.

repeated, refined methods of roentgenological examination.

Fifteen other cases [4] have been reported of arthralgia as the first symptom of bronchogenic carcinoma. Mendlowitz states that in an occasional case of osteoarthropathy, the pains in the extremities may precede x-ray changes in the bones. In reviewing the literature, however, I have been unable to find one case comparable to this, where, in the presence of clubbing and concomitant signs and symptoms of osteoarthropathy the radiological findings of periosteal elevation could not be demonstrated.

Case 2.—The patient, a 32-year-old white man, was first seen in the Cardiac Clinic of the New Haven Community Hospital in July, 1955. He gave a history of cyanosis since birth and clubbing and dyspnea for many years. Development was normal, and squatting had never been noted. In April, 1950, the patient was admitted to another hospital to determine the nature and possibility of surgical correction of his congenital heart disease. Pertinent physical findings at that time included marked cyanosis, clubbing of digits (Fig. 3), and plethora. The heart was slightly enlarged. The second pulmonic sound was louder than the second aortic sound. A systolic murmur of maximal intensity was heard over the region of the third to fourth intercostal space along the left sternal border.

Blood examination revealed hemoglobin 25 gm. per 100 cc.; red blood cells, 8,500,000 per cubic centimeter, and hematocrit, 78%. Cardiac fluoroscopy and films revealed moderate enlargement of the right ventricle and pulmonary arteries and slight enlargement of the right auricle and left ventricle. Angiocardiography showed simultaneous opacification of the right heart, left ventricle, and aorta. Pulmonary artery filling was prompt, with engorgement of the main artery and its branches. Electrocardiogram was characteristic of right ventricular hypertrophy. Cardiac catheterization demonstrated the presence of a high interventricular septal defect with progressive significant increases in oxygen content from the right auricle to outflow of right ventricle and to the pulmonary artery. The systolic pressure of the pulmonary artery equalled that of the right ventricle, excluding the possibility of pulmonic stenosis. The systolic pressure was approximately equal in the femoral and pulmonary arteries. On the basis of those studies, the diagnosis of Eisenmenger's complex was convincingly established.

The patient's over-all condition did not appreciably change until March, 1955, when he noted hot tender swelling of his left knee after minor trauma. Three weeks later similar involvement of the left wrist, and later of the right wrist, appeared. Salicylates afforded little relief, and he was treated with cortisone with gradual and partial subsidence of the pains, which recurred when the drug was stopped. He was referred by his physician to the Cardiac Clinic in July, 1955, for further investigation and treatment of his cardiac condition and arthritis.

At that time, physical examination and laboratory procedures pertinent to the cardiac lesion were

Fig. 4 (Case 2).—Note clubbing of toes, periarticular swelling of ankles, manifested by elastic sock impressions, and obliteration of malleoli.

Fig. 5 (Case 2).—X-ray of long bones of forearms illustrating pronounced cortical thickening and extensive periosteal proliferation.

similar to those of 1950. The possibilities of rheumatoid arthritis, rheumatic fever, and traumatic arthritis were considered. The white blood cell count was 6350, with 6% eosinophilia. C-reactive protein was 1+, antistreptolysin O titer, 200 units. A sensitized sheep red cell titer was less than 8 units.

The patient continued to experience chronic fleeting arthralgia of his knees and wrists, worse at the end of the day and in damp weather. His wrists ached on moderate exertion, and tender swelling of the right wrist was noted in April, 1956. He had no fever, malaise, weakness, or symptoms referable to the small joints. In May, 1956, soft-tissue swelling of the ankles and feet with mild pitting edema was evident (Fig. 4). There was no venous distention, hepatosplenomegaly, orthopnea, or nocturnal dyspnea. Hypertrophic osteoarthropathy was suspected on the basis of the arthralgia. Roentgenograms disclosed the following: moderate osteoporosis of the hands and wrists and soft tissue swelling of dorsal phalanges of all digits, slight narrowing of the joint space of the left knee, narrowing and irregularity of the sacroiliac articulations. There was marked periosteal proliferation of the tibia, ulna, radius, and fibula bilaterally (Fig. 5). Chest film revealed no significant change since July, 1955. No discrete pulmonary densities were seen.

Comment.—This case also shows how readily osteoarthropathy may simulate primary joint disease. The roentgen findings of involvement of the knee and sacroiliac joints were not unlike those seen with rheumatoid arthritis. This is of interest in view of the concept of Marie of more and more proximal skeletal involvement as the process advances.

As nearly as can be determined, two cases have previously been reported of uncomplicated congenital heart disease with clubbing and periosteal and synovial findings of hypertrophic osteoarthropathy. Bamberger's case [2] of a 7-year-old child with congenital pulmonic stenosis (associated with a diminutive right ventricle and a septal defect), like Shaw and Cooper's case [17] of interventricular septal defect, had unmistakable osteoarthropathy. Neither suggested the complication of bacterial endocarditis, although pulmonary tuberculosis was found at autopsy in the first case. The diagnosis of septal defect in the second case was made on clinical grounds alone. The patient now presented is then the first case of a well-documented congenital defect (Eisenmenger's complex) with secondary osteoarthropathy.

It is suggested that more cases probably exist with this association. Since hypertrophic osteoarthropathy is often asymptomatic, especially in early and slowly developing instances, routine films of the bones of the forearm and leg in cases of cyanotic congenital heart disease might uncover other cases.

Comment

In attempting to determine the relationship of digital clubbing to hypertrophic osteoarthropathy, one must define terms. By clubbing is meant the soft-tissue hypertrophy of the terminal phalanx, frequently with obliteration of the angle at which the nail takes origin from the finger. This has been aptly described elsewhere.[16] One must avoid confusing true clubbing with changes in curvature of the nail alone. The latter

may exist as a racial and familial trait with no clinical significance. Moreover, in seeking the presence of radiological confirmation of the diagnosis of osteoarthropathy, it is of little use to examine the fingers. Most roentgenologists agree that there are no bone changes of the terminal phalanges in this condition.[6,8,12]

Crump [18] recognizes three components of hypertrophic osteoarthropathy: clubbed fingers, a "toxic arthritis," and generalized periostitis. He states that two of these components can occur independently of the other, a situation that applies in Case 1 of this report. The previously discussed cases support the opinions expressed by both Locke and Mendlowitz that clubbing and hypertrophic osteoarthropathy are different manifestations of the same basic process and that any condition causing clubbing can eventually go on to cause full-blown osteoarthropathy.

Summary

Two cases are presented with digital clubbing and the clinical picture of hypertrophic osteoarthropathy.

The importance of recognizing this condition as a clue in early diagnosis of bronchogenic neoplasm is exemplified by the first case. Arthralgia, clubbing, and periarticular soft-tissue hypertrophy may precede the roentgenological evidence of periosteal proliferation.

The second case is of exceptional interest because the association of an uncomplicated congenital heart defect with hypertrophic osteoarthropathy has not been previously established.

Together they support the unitarian concept (Mendlowitz; Crump) relating true clubbing with arthralgia and periosteal changes as hypertrophic osteoarthropathy.

Dr. Massimo Calabresi, Chief of Cardiology, West Haven Veterans' Hospital, aided in this study.

Veterans' Administration Hospital (16).

REFERENCES

1. Marie, P.: De L'Ostéo-arthropathie hypertrophiante pneumique, Rev. méd., Paris 10:1, 1890.

2. Bamberger, E.: Über Knochenveränderungen bei chronischen Lungen- und Herzkrankheiten, Ztschr. klin. Med. 18:193, 1891.

3. Miller, E. R.: Carcinoma of the Thymus with Marked Pulmonary Osteoarthropathy, Radiology 32:651, 1939.

4. Berg, R., Jr.: Arthralgia as First Symptom of Pulmonary Lesions, Dis. Chest 16:483, 1949.

5. Vogel, A.; Blumenfeld, S., and Gutner, L. B.: Diagnostic Significance of Pulmonary Hypertrophic Osteoarthropathy, Am. J. Med. 18:51, 1955.

6. Temple, H. L., and Jaspin, G.: Hypertrophic Osteoarthropathy, Am. J. Roentgenol. 60:232, 1948.

7. Cushing, E. H.: Clubbed Fingers and Hypertrophic Pulmonary Osteoarthropathy, Internat. Clin. 2:200, 1937.

8. Compere, E. L.; Adams, W. E., and Compere, C. L.: Generalized Hypertrophic Pulmonary Osteoarthropathy, Surg. Gynec. & Obst. 61:312, 1935.

9. Locke, E. A.: Secondary Hypertrophic Osteo-Arthropathy and Its Relation to Simple Club-Fingers, Arch. Int. Med. 15:659, 1915.

10. Pattison, J. D., Jr.; Beck, E., and Miller, W. B.: Hypertrophic Osteoarthropathy in Carcinoma of the Lung, J. A. M. A. 146:783, 1951.

11. Jones, T. D.: Cyanosis and Clubbing of Fingers, New England J. Med. 205:940, 1931.

12. Pugh, D. G.: Pulmonary Osteoarthropathy: The Roentgenologic Diagnosis of Disease of Bones, in Golden, R.: Diagnostic Roentgenology, Baltimore, Williams & Wilkins Company, 1952, Vol. 2, p. 469.

13. Ray, E. S., and Fisher, H. P., Jr.: Hypertrophic Osteoarthropathy in Pulmonary Malignancies, Ann. Int. Med. 38:239, 1953.

14. White, P. D., and Sprague, H. B.: The Tetralogy of Fallot: Report of a Case in a Noted Musician, Who Lived to His Sixtieth Year, J. A. M. A. 92:787, 1929.

15. Mendlowitz, M.: Clubbing and Hypertrophic Osteoarthropathy, Medicine 21:269, 1942.

16. Schnitker, M. A.: Congenital Anomalies of the Heart and Great Vessels, New York, Oxford University Press, 1952, p. 68.

17. Shaw, H. B., and Cooper, R. H.: Pulmonary Hypertrophic Osteo-Arthropathy Occurring in a Case of Congenital Heart Disease! Lancet 1:880, 1907.

18. Crump, C.: Histologie der allgemeinen Osteophytose (Ostéoarthropathie hypertrophiante pneumique), Arch. path. Anat. 271:467, 1929.

19. Campbell, D. C.; Sacasa, C. F., and Camp, J. D.: Chronic Hypertrophic Osteoarthropathy, Proc. Staff Meet. Mayo Clin. 13:708, 1938.

20. Holt, J. F., and Hodges, F. J.: Significant Skeletal Irregularities of the Hands, Radiology 44:23, 1945.

21. Poppe, J. K.: Diagnostic Significance of Clubbed Fingers, Dis. Chest 13:658, 1947.

Pulmonary Nocardiosis Treated with Chloramphenicol

JULIO V. RIVERA, M.D., and JOSEFINA BARALT PEREZ, M.S., San Juan, P. R.

Human infections with aerobic Actinomyces which were formerly considered a rarity are being recognized with increasing frequency.[1-3] Over 57 cases have been reported from various regions of the world. Nine of the forty-two known strains of Nocardia have been isolated from human cases.[6]

The disease involves most frequently the lungs in the form of an acute bronchopneumonia, which may become chronic, with areas of consolidation and often involvement of the pleura. Healing of pulmonary lesions may occur by complete resolution, or fibrosis may follow. Metastatic lesions, apparently blood borne, may involve any organ but are especially frequent in the brain.[3,7] Cerebral symptomatology may be the initial or sole manifestation of the disease.[8]

Although the disease was almost always fatal in the past and still carries a high mortality rate (about 60%), since the introduction of effective chemotherapeutic and antibiotic agents a considerable proportion of the cases of the pulmonary form receiving adequate treatment have been cured or improved. Cerebral nocardiosis remains a uniformly fatal disease.

The following case is of interest because it is the first one reported from Puerto Rico and because of the successful result obtained by treatment with chloramphenicol.

Report of Case

This 65-year-old man was admitted to the hospital for the first time on June 6, 1955, with complaint of anorexia. He stated that on May 31, 1955, he had suddenly developed anorexia, nausea, and a feeling of emptiness in the abdomen. He restricted his diet to fluids but was able to continue ambulatory for several days. There also appeared an unproductive cough, which was not accompanied by chest pain, fever, or dyspnea. On the day of admission he felt chilly. He had lost 20 lb. during the present illness. History obtained from the patient's daughter revealed that he had had a cough for several months. Neither the patient nor his family had a history of previous pulmonary disease. A chest x-ray had been taken a few months before the present illness and was said to have been negative.

Physical examination on admission revealed an underdeveloped, poorly nourished, pale, elderly man who appeared chronically ill. Temperature was 100.4 F, and pulse was 80 per minute. Coarse and fine rales were heard over the whole left hemithorax posteriorly and in the upper third anteriorly. There was bronchial breathing in the region of the third left anterior intercostal space. Examination of the heart and abdomen was negative. There were surgical scars on the right groin. Clubbing of the fingers was present.

Laboratory Examinations.—RBC 4,510,000; hemoglobin 14.2 gm.; WBC 10,000; differential—neutrophils 84%, lymphocytes 16%. Urinalysis: 1+ albumin, occasional hyaline casts, and 1.020 specific gravity. VDRL microflocculation was negative. Sputum smears and cultures showed branching Gram-negative filaments. These organisms were identified as Nocardia asteroides. Serum bilirubin was 1.53 mg/100 cc. Erythrocyte sedimentation rate was 34 mm. in one hour (Wintrobe). Cephalin flocculation was 1+. Blood and bone marrow cultures were sterile.

Chest x-ray showed diffuse mottling throughout, especially in the right upper lobe and left lower lobe, which was interpreted as bronchopneumonia.

With a tentative diagnosis of bacterial pneumonia, the patient was started on 600,000 units of procaine penicillin daily without apparent benefit. Roentgenogram on June 9 showed extension of infiltration to the right lower and left upper lobes. Fever continued, and the patient became mentally confused. Neurological examination and electroencephalogram were normal. Because of the finding of Nocardia in the sputum and the presence of mental symptoms, lumbar puncture was performed. Spinal fluid showed no cellular or chemical ab-

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From Medical Service, San Patricio Veterans' Administration Hospital and School of Medicine, School of Tropical Medicine, University of Puerto Rico.

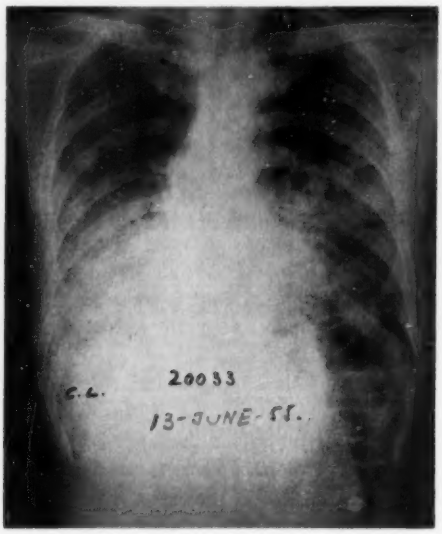

Fig. 1.—Chest film on June 13, 1955, showing mottled infiltrations in both upper and left lower lung fields and dense consolidation in the right lower lobe.

normalities and was sterile on culture. The organism (N. asteroides) present in the sputum was found to be sensitive to chlortetracycline. Administration of its anologue, tetracycline, together with sulfadiazine was associated with a temporary decrease in the fever but no improvement in clinical findings. A pleural friction rub became audible at the right lung base. Chest film (Fig. 1) showed some clearing of infiltrations in upper lobes and marked increase in the right lower lobe. A trial of potassium iodide was also unsuccessful. Under therapy with chloramphenicol, which was started on June 27, there was prompt improvement, with disappearance of fever and reduction in the amount of sputum. The organism became scanty but could still be identified in sputum smears. Gradually a severe anemia developed. Bone marrow studies showed slight hypocellularity. It was suspected that this anemia could be due to chloramphenicol, and for this reason the drug was discontinued temporarily. In spite of the administration of large doses of penicillin, there was a recurrence of fever and expectoration. The leukocyte count increased. Nocardia were again found abundantly in the sputum. Because of the rapid deterioration of patient's condition, chloramphenicol was again prescribed. A definite response was obtained. Although there was gradual clearing of the pulmonary infiltrations during the last month in the hospital, it was not anywhere near complete by the time of discharge. The anemia required the administration of several blood transfusions. Anorexia was a prominent feature, but it had improved somewhat during the last few weeks of the patient's stay. Patient was discharged on Sept. 16, 1955, to continue treatment at home. While at home he continued to do well. When last heard from, in December, 1955, he had gained all previously lost weight and was asymptomatic. Hemoglobin and leukocyte count had returned to normal. Chest x-ray showed residual fibrotic changes. Expectoration had ceased, so that it was not possible to obtain a specimen for bacteriologic study.

Bacteriological Studies

The sputum was abundant and purulent. Smears of sputum showed Gram-positive branching filaments beaded with granules. Sometimes the filaments appeared Gram-negative and studded with Gram-positive granules. These forms were predominant and abundant and highly suggestive of an Actinomyces. In smears stained by Ziehl-Neelsen's method, only a few filaments showed feebly acid-fast staining properties. Because of the well-known variability in acid-fastness of Nocardia species, a modified acid-fast stain was used which consisted in decolorization with 1% aqueous sulfuric acid instead of 3% acid alcohol.[3] Many branching beaded acid-fast filaments were then observed.

Cultures on heart-infusion agar enriched with rabbit blood showed an abundant, almost pure growth of a Nocardia-like organism after 48 hours' incubation at 37 C. Colonies appeared

Fig. 2.—Chest film on Dec. 10, 1955, showing residual changes, particularly at the right lung base.

raised, dry, and wrinkled, becoming star-like and yellowish-cream in color on further incubation. They were adherent to the medium, of tough consistency, and difficult to emulsify. Gram stain of colonies showed irregularly stained beaded filaments and bacillary forms. On the same culture, some colonies had a chalky surface. The two types of colonies were subcultured to Sabouraud's agar slants, and on incubation at room temperature the yellowish-cream colonies developed a coral pigmentation and the chalky ones remained white. The growth on Sabouraud's agar at room temperature was slower than on blood agar at 37 C.

In vitro sensitivity tests using Difco sensitivity discs were performed with the cultures, and the results were as follows: very sensitive to chlortetracycline, oxytetracycline, tetracycline, sulfadiazine, and trisulfapyrimidines; slightly sensitive to erythromycin; resistant to chloramphenicol, penicillin, polymyxin B, and streptomycin.

Animal inoculations showed that the organism was pathogenic for mice and guinea pigs. Intraperitoneal inoculation of guinea pigs with 1 ml. suspension of the organism in mucin induced death in from three to five days. Smears from peritoneal lesions showed acid-fast branching filaments. Five out of five mice died over a two-week period following intraperitoneal inoculation without mucin, and the organism was recovered in subcultures.

The morphology of the organism and its partially acid-fast staining properties, mode of development, and growth characteristics mark this organism as N. asteroides. The chalky culture is probably a variant of N. asteroides.

Comment

Nocardia (actinomycetes) are taxonomically intermediate between the bacteria and the fungi. Many of their morphological and biochemical characteristics are intermediate between the two groups.[6] The clinical features of human infections as seen in this and in other reported cases certainly are similar to what one might expect in a bacterial infection.

It has been repeatedly stated that pulmonary nocardiosis may be easily confused with tuberculosis.[3,6] This is undoubtedly true of the chronic form of nocardiosis, especially if one considers the possible confusion of broken Nocardia filaments with tubercle bacilli on the examination of direct smears of sputum stained by the acid-fast technique. On the other hand, in the more acute form or early in the disease, pulmonary nocardiosis resembles other bacterial diseases more. The rapid progression of symptoms, high fever, polymorphonuclear leukocytosis, profuse purulent expectoration, and relatively rapidly changing roentgen picture suggest an acute bacterial infection. There is no particular predominance of upper-lobe involvement as is characteristic of tuberculous infection. On the other hand, the course of the disease is more prolonged than that usually seen in most bacterial pneumonias.

The diagnosis of pulmonary nocardiosis is a relatively simple one if this condition is kept in mind in the presence of chronic or acute pulmonary infections. An alert bacteriologist should have no difficulty in isolating and identifying this organism by the usual techniques.

There is no doubt about the etiological importance of N. asteroides in the case herein reported. The organism was found to predominate in numerous sputum specimens obtained, and its abundance in the secretion correlated well with the clinical course. The pathogenicity of the organism was substantiated by animal inoculations.

Because of the infrequency of human nocardiosis, conclusions as to the effectiveness of various agents have been based on individual case reports, and comparative studies have not been possible. In vitro and animal-inoculation studies have been infrequent and the results variable. To date sulfadiazine has been found to be the most successful drug. In most of the reported cases recovery has been attributed to this agent, although it has been frequently used concomitantly with antibiotics, surgical procedures, and other supportive measures. On the other hand, certain strains of Nocardia have been found resistant.[9] The strain isolated from this patient appeared to be susceptible to sulfadiazine in vitro. No apparent benefit resulted from its administration, but this may have been due to the small dosage used. Penicillin and chlortetracycline in adequate doses did not benefit this patient.

Treatment of human nocardiosis with chloramphenicol has been reported infrequently. In combination with penicillin and oxytetracycline it did not appear to alter the course of a case of the generalized disease reported by Wichelhausen et al.[5] A case of actinomycosis (A. israeli) successfully treated with chloramphenicol has been reported.[10] In vitro and animal studies have shown sensitivity of some strains, resistance of others.[2-5,11-14] The in vitro studies of the strain isolated from this case did not correlate with the definite clinical response which was obtained twice. This lack of correlation has been reported in infections with other organisms. Unfortunately, we have been unable to carry out animal-protection studies.

The importance of prolonged treatment with whatever agent is found beneficial is well illustrated by this and other cases in the literature.[2,9] When therapy is omitted too soon recurrence frequently follows.

Summary

A case of pulmonary nocardiosis is reported. It is the first one described in Puerto Rico. Treatment with penicillin, tetracycline, and small doses of sulfadiazine was unsuccessful. Although the organism was resistant to chloramphenicol in vitro, administration of this drug proved beneficial. Chloramphenicol appears to deserve further trial in the treatment of this still highly fatal disease.

Miss Charlotte C. Campbell, Mycologist, Walter Reed Army Institute of Research, Washington, D. C., and Dr. Gladys Torres, Mycologist, University of Puerto Rico School of Medicine, confirmed the identification of the organism and performed the animal inoculations.

Veterans' Administration Center, P. O. Box 4424.

REFERENCES

1. Bobbitt, O. B.; Friedman, I. H., and Lupton, C.: Nocardiosis: Report of 3 Cases, New England J. Med. 252:893-897, 1955.

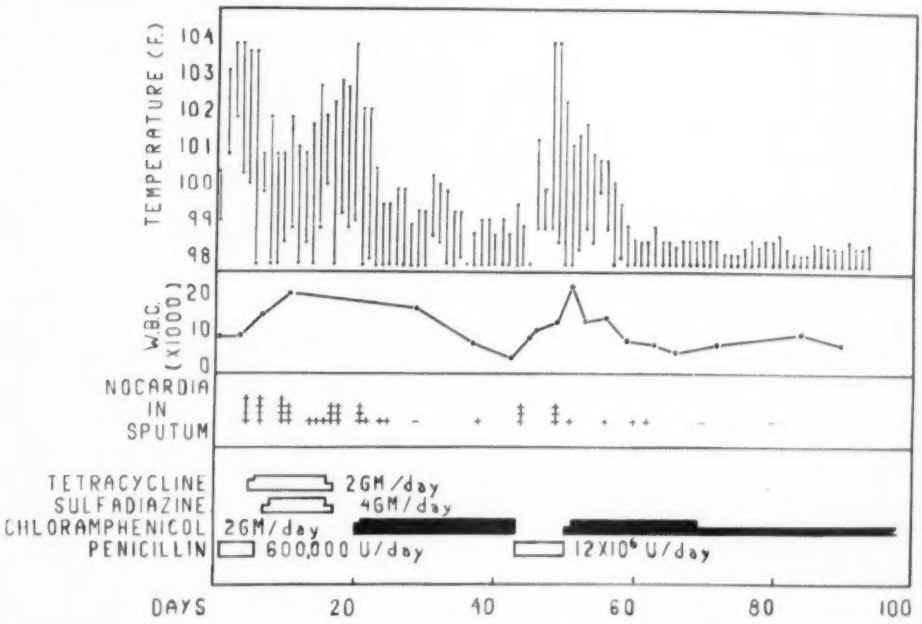

Fig. 3.—Clinical course, laboratory findings, and therapy.

2. Kohn, P. M.; Tager, M.; Siegel, M. L., and Ashe, R.: Aerobic Actinomyces Septicemia: Report of Case, New England J. Med. 245:640-644, 1951.

3. Cruz, P. T., and Clancy, C. F.: Nocardiosis: Nocardial Osteomyelitis and Septicemia, Am. J. Path. 28:607-627, 1952.

4. Bernstein, I. L.; Cook, J. E.; Plotnick, H., and Tenczar, F. J.: Nocardiosis: Three Case Reports, Ann. Int. Med. 36:852-863, 1952.

5. Wichelhausen, R. H.; Robinson, L. B.; Mazzara, J. R., and Everding, C. J.: Nocardiosis: Report of a Fatal Case, Am. J. Med. 16:295-303, 1954.

6. McQuown, A. L.: Actinomycosis and Nocardiosis, Am. J. Clin. Path. 25:2-13, 1955.

7. Kaufman, N., and Prieto, L. C., Jr.: Cerebral Nocardiosis: Report of Case with Necropsy, A. M. A. Arch. Path. 53:379-384, 1952.

8. Erchul, J. W., and Koch, M. L.: Cerebral Nocardiosis with Coexistent Pulmonary Tuberculosis: Report of a Fatal Case, Am. J. Clin. Path. 25:775-781, 1955.

9. Hager, H. F.; Migliaccio, A. V., and Young, R. M.: Nocardiosis: Pneumonia and Empyema Due to Nocardia Asteroides, New England J. Med. 241:226-231, 1949.

10. Littman, M. L.; Paul, J. S., and Fusillo, M. H.: Treatment of Pulmonary Actinomycosis with Chloramphenicol: Report of Case, J. A. M. A. 148:608-612, 1952.

11. Littman, M. L.; Phillips, G. E., and Fusillo, M. H.: In Vitro Suspectibility of Human Pathogenic Actinomycetes to Chloramphenicol (Chloromycetin), Am. J. Clin. Path. 20:1076-1078, 1950.

12. Runyon, E. H.: Nocardia Asteroides: Studies of Its Pathogenicity and Drug Sensitivities, J. Lab. & Clin. Med. 37:713-720, 1951.

13. Strauss, R. E.; Kligman, A. M., and Pillsbury, D. M.: The Chemotherapy of Actinomycosis and Nocardiosis, Am. Rev. Tuberc. 63:441-448, 1951.

14. McLean, I. W., Jr.; Schwab, J. L.; Hillegas, A. B., and Schlingman, A. S.: Symposium on Antibiotics: Susceptibility of Micro-Organisms to Chloramphenicol (Chloromycetin), J. Clin. Invest. 28:953-963, 1949.

Progress in Internal Medicine

Differential Diagnosis and Treatment in Hemorrhagic Disease

JESSICA H. LEWIS, M.D., and PAUL DIDISHEIM, M.D., Pittsburgh

Differential diagnosis and treatment of excessive bleeding rest upon an understanding of normal hemostatic mechanisms. Although all of the intricacies of this complicated physiological process are not fully understood, enough information is available to form a theory. The simple diagram (Fig. 1) presents the main facets

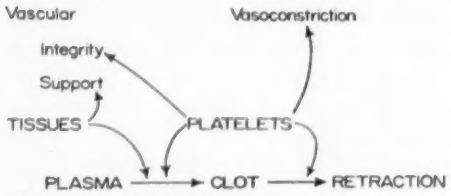

Fig. 1.—A simplified representation of normal hemostatic mechanisms.

of normal hemostasis. The steps probably occur simultaneously but it is convenient to consider them in four sections: vascular, tissue, platelet and plasma.

Steps in Normal Hemostasis

Vascular.—Intact blood vessels are obviously necessary to contain the circulating blood. In addition, blood vessels, particularly those with muscular walls, respond to mechanical (injury) or chemical stimuli (see serotonin, below) with constriction, thus reducing blood flow to an injured area.

Tissue.—Normal tissues play a multiple role. First, all of the many circulating factors important in maintenance of fluidity as well as formation of the blood clot are formed in various tissue sites (Table 1). Second, when tissue is damaged, thromboplastic factors are released and probably initiate coagulation. Third, skin, elastic, collagenous and fatty tissues serve to support blood vessels and to protect them from injury.

Platelet.—Normally, platelets circulate as discrete cells, and it has been postulated that they have a function in plugging minute vascular leaks. In the presence of thrombin and other serum components, platelets agglutinate, forming a "white thrombus," which may be sufficient in itself to obstruct a bleeding point or may initiate the formation of a fibrin clot.

In addition platelets contain at least four factors which aid hemostasis.

1. Vasoconstrictor Factor, or Serotonin: This is released from agglutinated platelets and, diffusing into the local area, constricts not only the injured vessel but other adjacent vessels.

2. Thromboplastic Factor: This, together with plasma thromboplastic factors, plays an essential role in the formation of the fibrin clot.

3. Accelerator Factor: This has an action similar to plasma proaccelerin, and, in fact, may be simply plasma proaccelerin adsorbed onto the platelet.

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From the Department of Medicine, University of Pittsburgh School of Medicine.

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TABLE 1.—*Origin and Nature of Various Coagulation Factors*

Factor	Origin	Nature
Platelets	Megakaryocytes (bone marrow, lungs ?)	Complex cellular structure (hyalomere and granulomere)
Serotonin	Enterochromaffin cells (gastrointestinal tract, etc.)	5-hydroxytryptamine creatinine sulfate
Thromboplastin	?	Phospholipid
Plasma		
Prothrombin	Liver	Glycoprotein, in α to α_2 globulin fraction; molecular weight = 62,000
Proconvertin	Vitamin K essential; antagonized by bishydroxycoumarin (Dicumarol) type drugs	β-globulin
PTC		β-lipoprotein
Proaccelerin	Liver ? Bone marrow ?	β_2-globulin
AHF	Reticuloendothelical system ?	Globulin
PTA	?	β-globulin
Fibrinogen	Liver ?	Fusiform protein 50 by 600 A.; molecular weight = approximately 400,000
Heparin	Mast cells	Polysaccharide-polysulfuric acid ester
Tissue		
Thromboplastin	Brain, lung, other tissues	Complex mixture including lipoproteins and phospholipids

4. Retractor Factor: This is responsible for clot retraction.

Plasma.—Plasma contains a number of proteins present in circulating blood as inert or precursor substances, which become activated after blood is shed. In addition there are also a number of inhibitors to the active factors, which may check the coagulation reaction if it is initiated in vivo. The trigger mechanism by which the inert or precursor substances are initially activated is not fully understood. An acceptable, but not proven, theory suggests that when blood is shed and is exposed to a foreign surface plus air, this exposure serves to activate one of the proteins which, in turn, activates or reacts with another, setting up a chain reaction eventually evolving thrombin, which converts soluble fibrinogen into insoluble fibrin. In addition to exposure to foreign surface and air, the shedding of blood usually involves mixture with tissue juice, which contains thromboplastin, a potent activator.

In considering the individual reactions involved in fibrin clot formation it is convenient to divide them into three groups: (1) thromboplastin formation; (2) thrombin formation; (3) fibrin formation. The diagram (Fig. 2) summarizes the roles of the various factors in the formation of the plasma clot. Table 2 lists synonyms for these coagulation factors and selected references.

TABLE 2.—*Plasma Coagulation Factors: Synonyms and References*

Factor	Synonym	Reference
Thromboplastin formation		
AHF	Antihemophilic globulin (AHG)	1, 2
	Thromboplastinogen	3
	Hemophilic factor A	
PTC	Plasma thromboplastin component	4, 5
	Christmas factor	6
	Hemophilic factor B	
PTA	Plasma thromboplastin antecedent	7
	Hemophilic factor C	
?	Other thromboplastic factors	
	4th factor	8
Hageman	Hageman factor	9
Thrombin formation		
Prothrombin (ProT)		9a
Proconvertin (ProC)	Factor VII	10
	SPCA	11
	Stable factor	
Proaccelerin (ProA)	Factor V (parahemophilia)	12
	Plasma Ac globulin	13
	Labile factor	14
Other factors	Factor X	15
	Stuart factor	16, 17
Fibrin formation		
Fibrinogen		

Hemorrhagic Diseases

From the foregoing discussion it may be presumed that excessive bleeding can result from a large number of different abnormalities, and this, indeed, is the case. There are two general types of bleeding tendency:

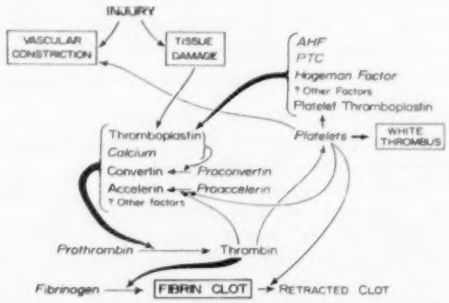

Fig. 2.—Factors involved in blood coagulation. Those present in circulating plasma are italicized.

primary, which is usually congenital, often familial, and almost always represents a single deficiency or abnormality, and secondary, or acquired, which is associated with some underlying disease process and often involves multiple abnormalities. History and physical examination are of prime importance in distinguishing between the two.

Primary (congenital) and secondary (acquired) hemorrhagic diseases may be considered under the following categories:

Congenital Vascular Purpura.—Under this heading we have grouped a number of conditions which may be separate entities. Abnormalities in vascular structure may consist of localized dilatations, tortuosities, and thinnings of the vessel walls as in angiomata and hereditary hemorrhagic telangiectasis (Osler-Weber-Rendu disease). The latter is diagnosed by observation of lesions most commonly seen on finger tips, toes, ears, lips, tongue, and nasal mucosa. The most common symptoms are epistaxis, hemoptysis, hematemesis, and melena. Hemostatic tests are generally normal. Generalized vascular purpura, often called by the confusing term pseudohemophilia, appears to be due to a widespread capillary defect and is characterized by a prolonged bleeding time and symptoms of easy bruising, epistaxis, and postoperative bleeding. The tourniquet test may be positive, and, in roughly 50% of these patients, a decrease in the plasma level of antihemophilic factor (AHF) is observed. This decrease is in the range of 10% to 50% of normal, far higher than the levels seen in classical hemophilia. All other hemostatic tests are usually normal.

Acquired Vascular Purpura.—This includes bleeding from gross lesions, e. g., dissecting aneurysm, and from small vessels, e. g., scurvy, Schoenlein-Henoch purpura, reactions to drugs, and toxins. As a rule the blood is normal coagulation-wise, and only an occasional positive tourniquet test is seen. In purpura related to drug sensitivity the lesions are generally most prominent over the lower extremities.

Tissue Abnormalities.—Poor blood vessel support due to abnormal elastic and collagenous tissue in Ehlers-Danlos syndrome (cutis hyperelastica) appears to be responsible for the tendency to easy bruising in this condition.

Congenital Platelet Purpura.—This may be of two types: thrombocytopenic or thrombocytopathic. 1. True congenital thrombocytopenia is rare but has occasionally been observed as a familial trait. Thrombocytopenia in the newborn has been reported in association with idiopathic thrombocytopenia in the mother and in what appears to be a platelet antigen-antibody reaction possibly analogous to the red cell antigen-antibody reaction of erythroblastosis fetalis. 2. The term thrombocytopathia indicates that platelets are normal in number, sometimes abnormal in appearance, and deficient in one or more of their functions. This condition may be confused with congenital vascular purpura unless the platelets are isolated and tested for each factor. The condition is often familial but the pattern of transmission is not clearly established.

Acquired Platelet Purpura.—1. Thrombocytopenia is probably the most common cause of a hemorrhagic tendency and may result from decreased production or increased peripheral destruction of platelets. Thrombocytopenias associated with bone marrow disease (e. g., leukemia), certain toxins, infections and allergies, and, perhaps, with splenic disease are due primarily to lack of platelet formation or release from bone marrow, while thrombotic thrombocytopenic purpura and certain drugs act through peripheral mechanisms of increased destruction. Idiopathic thrombocytopenic purpura (ITP) may well combine both mechanisms. 2. Acquired thrombocytopathia may be present when platelets are poor in function and either increased in number, e. g., some cases of polycythemia vera, leukemia, or thrombocytosis, or normal in number, e. g., uremia and some cases of cirrhosis of the liver.

Congenital Plasma Purpuras.—This large group includes the hemophilias, afibrino-

genemia, and those disorders with prolonged prothrombin times. For the purpose of this discussion hemophilia is defined as a congenital hemorrhagic disease in which the prothrombin time and fibrinogen level are normal and the clotting time, prothrombin consumption, and thromboplastin generation are abnormal or normal depending upon the severity of the deficiency. At least three types, (*a*) AHF, (*b*) PTC, and (*c*) PTA, may be clearly defined, as the deficient proteins are completely different. Other types of hemophilia have been described, but the characteristics of the deficient proteins have not been clearly defined. Hemorrhagic symptoms vary with the severity of the clotting factor defect. The most common symptoms are easy bruising, postoperative bleeding, hemarthrosis, and hematuria. Another deficiency, that of Hageman factor, may also be considered in this group. Patients with this deficiency show prolonged clotting times and abnormal prothrombin consumption and thromboplastin generation but do not show any bleeding tendency. No reasonable explanation has yet been offered for this.

Congenital afibrinogenemia is very rare and is readily diagnosed by complete lack of blood clot formation, even on addition of a concentrated thrombin solution. The symptoms are similar to hemophilia, but may be less severe.

Congenital conditions in which a prolonged prothrombin time (Quick) is observed have been recorded in a number of instances. At least two, and perhaps three, factors other than prothrombin may be responsible. Proaccelerin, proconvertin and Stuart factor have been defined. Familial tendency has been described in each deficiency, but sufficient data are not yet available to establish the patterns of inheritance in these conditions.

Acquired Plasma Purpuras.—Bleeding manifestations as complications of systemic disease are very common and derive from deficiencies of one or more coagulation factors or excesses of inhibitors. Table 3 lists some conditions in which bleeding is commonly seen, together with the usual laboratory findings.

An additional word should be included about inhibitors. A number of patients have been described in whom inhibitors to various coagulation factors, e. g., thromboplastin, AHF, PTC, have developed either *de novo* or in the presence of preexisting hemophilia, and in many instances these have appeared to be related to previous transfusions, preg-

TABLE 3.—*Common Abnormalities in Secondary Hemorrhagic Disease*

Primary Condition	Vascular Damage	Thrombopenia	Thrombopathia	Plasma Deficiency of: ProT ProC PTC	Plasma Deficiency of: ProA	Plasma Deficiency of: Fibrinogen	Presence of Inhibitors
Scurvy	+						
Schoenlein-Henoch	+						
Drug reactions	±	±					
Infections	±	±					
Allergens	±	±					
ITP	±	+					
Hypersplenism		+					
Radiation		+					
Multiple transfusions		+					
Thrombotic thrombopenia	+	+					
Bone marrow disease		+			+		
Leukemia		+			+		+
Polycythemia vera			±		±		
Thrombocythemia			+		±		
Uremia			+				
Cirrhosis, liver			±	+	+		
Hem. disease newborn				+			
Sprue, some gastrointestinal diseases				+			
Biliary obstruction				+			
Prolonged antibiotic therapy				+			
Bishydroxycoumarin (Vit. K antagonists)				+			
Dis. lupus erythematosus							+
Abruptio placentae, etc.					+	+	+
Shock, Ca prostate					+	+	+

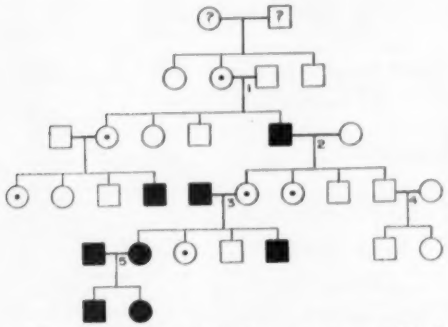

Fig. 3.—Sex-linked inheritance in hemophilia A and B. Open square or circle indicates a normal male or female; circle with dot, a carrier female; black square or circle, a hemophiliac male or female.

nancies, or other conditions which might stimulate antibody formation. In others, active fibrinolysin may appear in the blood and destroy circulating coagulation factors, proaccelerin, and fibrinogen in particular. This appearance of fibrinolysin is manifest when shed blood clots and the clot subsequently dissolve. The mechanisms by which this enzyme appears are not clearly understood, but its presence may occasionally be demonstrated in shock, certain complications of pregnancy and delivery, pulmonary surgery, metastatic carcinoma of the prostate, and severe liver disease.

Differential Diagnosis

Family History.—A history of bleeding in other members of a family is obtained in about 75% of congenital bleeders. Sex-linked inheritance (Fig. 3), in which the disease is usually manifest in males, is the common pattern in both hemophilia A and hemophilia B. The asymptomatic female carrier can transmit the overt disease to half of her sons and the carrier state to half of her daughters. All daughters of a hemophiliac male will be carriers, and all sons will be normal. Progeny from a mating between a carrier and a hemophiliac may be expected to be of four types: hemophiliac female, carrier female, normal male, or hemophiliac male. Lastly, if both parents are hemophiliac all progeny may be expected to be bleeders. Transmission by either sex as a dominant characteristic is found in some of the vascular purpuras (hereditary hemorrhagic telangiectasia). Simple recessive and dominant genetic patterns with variable penetrance have been described, but sufficient data are not yet available to determine the exact pattern in each deficiency.

History and Physical Examination.—Onset of hemorrhagic symptoms may date from umbilical cord bleeding, circumcision, or hemorrhagic manifestations in early childhood. Severity of bleeding varies greatly among different persons, although it is usually similar in all affected members of any given family and correlates fairly well with laboratory findings. It should be emphasized that patients suffering from a single deficiency, e. g., AHF or PTC, may vary clinically from very severe to very mild, and show corresponding plasma AHF or PTC levels of 0 to 10%. Thus, severity of symptoms does not help in differentiating the type of deficiency. Type of bleeding is of some aid in differential diagnosis, particularly between plasma disorders and disorders of platelets or blood vessels. Thus, in the hemophilias large ecchymoses, muscular hematoma, and hemarthroses are common, while in the thrombocytopenias petechiae, epistaxis, and bleeding from the gums and other mucous membranes are more characteristic. Hemophilia A and B cannot be distinguished on the basis of history. Physical examination may prove valuable in distinguishing between various types of bleeding. Special care should be taken in examining the skin and mucous membranes for vascular abnormalities, petechiae, perifollicular petechiae (scorbutic), and large ecchymoses. In small children a subcutaneous nodule is frequently palpable in the center of a hematoma. Hemarthroses and ankyloses are common in hemophilia A and B and rare in other conditions.

Laboratory Examination.—The usual laboratory techniques are very helpful in distinguishing most types of hemorrhagic disease (Table 4). In the hemophilias, if the deficiency is severe enough to cause a

TABLE 4.—*Common Abnormalities in Primary Hemorrhagic Disease* *

Tests	Bl. T	T. T.	Pl. C.	Cl. Ret.	Cl. T.	ProT. Cons.	Tpln. Gen.	ProT. Time	Special Assays
Cong. vascular purpura	±	±	0	0	0	±	±	0	±
Thrombocytopenia	+	+	+	+	0	+	+	0	0
Thrombocytopathia	±	±	0	±	0	±	±	0	+
Hemophilia A (AHF)	0	0	0	0	+	+	+	0	+
Hemophilia B (PTC)	0	0	0	0	+	+	+	0	+
Hemophilia C (PTA)	0	0	0	0	+	+	+	0	—
Hageman factor deficiency	0	0	0	0	+	+	+	0	+
Hypoprothrombinemia	0	0	0	0	+	0	0	+	+
Hypoproconvertinemia	0	0	0	0	±	±	0	+	+
Stuart factor deficiency	0	0	0	0	+	+	+	+	+
Hypoproaccelerinemia	0	0	0	0	+	+	+	+	+
Afibrinogenemia	0	0	0	No clot	No clot	0	0	No clot	+

* Bl. T. indicates bleeding time; T. T., tourniquet test; Pl. C., platelet count; Cl. Ret., clot retraction; Cl. T., clotting time; ProT. Cons., prothrombin consumption; Tpln. Gen., thromboplastin generation; ProT. Time, prothrombin time; +, abnormal; 0, normal. The column headed "special assays" indicates whether a more definitive diagnosis can be made by special specific assays.

prolonged clotting time, the effects of various added materials may be tested and will aid in differentiating the type (Table 5). Thus, when 1 ml. of patient's blood is added to 0.1 ml. of normal plasma all deficiencies are corrected; if $BaSO_4$-treated plasma is used AHF, PTA, and Hageman deficiencies

TABLE 5.—*Differentiation of Hemophilias* *

Type of Hemophilia	Reagent		
	Normal Plasma	Normal Serum	$BaSO_4$ Normal Plasma
A (AHF)	+	0	+
B (PTC)	+	+	0
C (PTA)	+	+	+
Hageman	+	+	+

* Corrective effects on clotting time and prothrombin consumption. 1 ml. patient's blood added to 0.1 ml. reagent.

are corrected, and if old serum is used, PTC, PTA, and Hageman deficiencies are corrected. Mild deficiencies cannot be determined in this way, and actual titers for AHF, PTC, or other factors are necessary; methods for carrying out these titers are described in the Appendix. When the prothrombin time is prolonged, the tests in Table 6 may be of value in determining which factor is at fault. Again, actual assays (Appendix) are usually more valuable.

Treatment

Methods of treatment (Table 7) may be divided into specific measures, which attempt to replace the missing factor or suppress the offending inhibitor, and nonspecific measures, which try to stop the flow of blood and prevent future injury. The only specific measure in vascular disease is removal of the lesion, which may be possible (by excision or cautery) if the lesion be localized. In thrombocytopenia associated with poor platelet production or in thrombocytopathia the infusion of normal fresh (or lyophilized [18]) platelets may be of temporary value but is not yet practical over extended periods. In thrombocytopenia associated with an increased rate of platelet destruction removal of the spleen and/or therapy with corticotropin and cortisone or its analogues may prove life-saving. In the plasma purpuras fresh whole blood or plasma may be used in all cases except those in which inhibitors are present. In the latter, blood

TABLE 6.—*Differential Diagnosis in Patients with Prolonged Prothrombin Times* *

Deficiency	Quick Test	Prot. Cons.	Tpln. Gen.	2-Stage Prot.	Corrected by	
					Aged Plasma	Fresh $BaSO_4$ Plasma
Prothrombin	Long	†	? N	ABN	+	0
Proaccelerin	Long	ABN	ABN	N	0	+
Proconvertin	Long	N	N	N	+	0
Stuart factor	Long	ABN	ABN	N	+	0

* ProT. Cons. indicates prothrombin consumption; Tpln. Gen., thromboplastin generation; 2-Stage ProT., 2-stage prothrombin assay, Method II.
† Because of the low plasma prothrombin level, calculation of prothrombin consumption is valueless.

TABLE 7.—*Therapy in Hemorrhagic Disease*

Disease	Therapeutic Measures
Vascular purpura	Local treatment, cold, vasoconstrictors, flavonoids, corticotropin, (ACTH), cortisone
Thrombocytopenia	
Decreased production	Platelet-rich plasma, platelet concentrates
Increased destruction	Splenectomy, cortisone, corticotropin
Thrombocytopathia	? Platelet concentrates
Hemophilia A	Fresh plasma, AHF fraction
Hemophilia B	Old plasma, serum, PTC fraction
Hemophilia C	Plasma
Hypoprothrombinemia, Hypoproconvertinemia, Hypoproaccelerinemia	Plasma, fractions; Vitamin K (in acquired); Fresh plasma
Fibrinogen	Plasma, fibrinogen fractions
Circulating inhibitors	? Cortisone; washed red cells as needed
Circulating fibrinolysin	Plasma, antiproteases

transfusion may act as a stimulus to the formation of more inhibitor and should be avoided if possible, and washed red cells should be used to replace those lost. The little information available as to the half-lives of the various clotting factors suggests a half-life of four hours for AHF and two to four days for PTC. Thus, when beneficial effects are expected from transfused plasma, it should be given at frequent intervals, every four to eight hours in hemophilia A, daily in hemophilia B. Volumes of plasma calculated to raise the level of the deficient factor to 10% should be employed. Freshly drawn blood, or plasma quickly frozen following collection, is essential in hemophilia A, but blood or plasma stored up to two weeks is at least as satisfactory as fresh in hemophilia B. Good dental prophylaxis can avoid much difficulty in the hemophilias. If dental extraction or other surgery is required, repeated plasma transfusions should be administered aiming at a level of 10% of the deficient factor before, during, and for several days following operation. If close attention is paid to blood and plasma volume, the only contraindication to repeated transfusion is the possibility that the patient might develop an inhibitor; this can be tested for (Appendix), and should it arise, plasma should be withheld. Much research is being directed toward the preparation and preservation of plasma fractions, each containing one of the various clotting factors. Such fractions should prove of great benefit and possibly be of prophylactic value. Fibrinogen is available now in relatively pure and stable state.

Local nonspecific measures to stop bleeding are very valuable. Applications of cold to joints, bleeding gums, or teeth (Popsicles, etc.), or other bleeding surfaces, and of pressure when the bleeding point is accessible may control the hemorrhage. Occasionally the topical application of the following agents is also helpful: thrombin, thromboplastin, absorbable gelatin sponge (Gelfoam), or epinephrine. In acute hemarthroses the position the patient assumes is the least painful one, that of semiflexion; care should be taken that ankylosis in this position is not allowed to develop.

Summary

Excessive bleeding is a common symptom and may be a manifestation either of primary hemorrhagic disease or of a number of acquired disorders. Many diagnostic methods are now available, and in most instances the exact cause of the bleeding may be determined. Appropriate treatment is dependent upon proper diagnosis.

Appendix

Materials

Saline.—0.85% NaCl.

Buffered Saline.—9 parts saline plus 1 part imidazole buffer,[19] pH 7.3.

Calcium Thromboplastin.—Thromboplastin extract (Simplastin) (Warner, Chilcott Co.) or equal parts of 0.02 M $CaCl_2$ and thromboplastin (Solu-Plastin) (Schieffelin & Company) maintained at 37 C during test periods. The remaining materials are prepared in large batches, divided into small lots, and stored at −20 C.

Fibrinogen.—1% Armour Bovine Fraction I, treated with $BaSO_4$ (1 gm/100 ml.). For each day's assays a new bottle is thawed and diluted by adding 2 vol. buffered saline.

Prothrombin.—Bovine asbestos filtered plasma (as for proconvertin substrate) is treated with $BaSO_4$ (10 gm/100 ml.). The $BaSO_4$ collected by centrifugation, washed 4 times with saline and eluted with one-tenth the original plasma volume of 0.2 M sodium citrate and this eluate dialyzed against buffered saline.

Proconvertin.—Serum obtained from recalcified oxalated bovine plasma after standing at 4 C for

18 hours is treated with $BaSO_4$ (10 gm/100 ml.). After sedimentation the $BaSO_4$ is washed four times with saline and eluted with one-fifth the original plasma volume of 0.2 M sodium citrate and the eluate dialyzed against buffered saline.

Accelerin.—$BaCO_3$ (4 gm/100 ml.) treated bovine serum.

Prothrombin Substrate.—$BaSO_4$ (10 gm/100 ml.) treated bovine plasma mixed with one-tenth of its volume of proconvertin.

Proconvertin Substrate.—Oxalated beef plasma passed twice through Seitz filter pads containing 20% asbestos. (Once through 20% and once through 30% has also been used). This plasma then contains fibrinogen and proaccelerin in normal amounts, almost no proconvertin, and about 60% prothrombin. It may be used as is or fortified by addition of purified prothrombin sufficient to bring content to 100%.

Proaccelerin Substrate.—Aged normal human plasma. (In aging, we freeze, thaw, incubate at 4 C for about two weeks, divide into lots, and store frozen). Prothrombin (Quick) time on this plasma should be 50 seconds or longer and prothrombin content approximately 100%.

AHF Substrate.—Blood from a hemophiliac (hemophilia A) with a clotting time of 60 minutes or longer and negligible prothrombin consumption is obtained with a No. 19 needle and siliconed syringes and mixed with one-tenth part 0.1 M sodium citrate. After centrifugation (in plastic or siliconed tubes), the plasma is removed, distributed in 1 ml. lots, and stored frozen in plastic tubes. Fresh lots are obtained every four months.

PTC Substrate.—Plasma obtained as above from a proven case of PTC deficiency.

Hageman Factor Substrate.—Plasma obtained as above from a proven case of Hageman Factor Deficiency.*

Standard Normal Plasma.—Pooled normal oxalated plasma.

Standard $BaSO_4$-Citrate Eluate.—Normal pooled plasma is absorbed with $BaSO_4$ (10 gm/100 ml.) for 10 minutes at room temperature. After centrifugation the $BaSO_4$ is washed with distilled water and eluted with one-third of the plasma volume of 0.2 M sodium citrate.

Methods

Tourniquet Test.—This test was designed to measure capillary strength. The forearm is examined for petechiae and a circle (quarter size) drawn on the flexor surface immediately below the antecubital fossa. Sphygmomanometer cuff is applied and maintained inflated at 70-80 mm. Hg (must be below systolic pressure) for seven minutes. After removal of cuff, arm is elevated for three minutes and then observed for petechiae. Those in circle are counted and extensor surface examined.

Interpretation: Number in counted area: 0-10=negative, 10-20=+, 20-30=++, 30-40=+++, >40=++++. Numerous petechiae on extensor surface and flexor surface including wrist=++++. Large perifollicular petechiae predominantly on extensor surface suggest scurvy.

Normal Range: 0-15 petechiae=negative or +.

Abnormal: Thrombocytopenia, thrombocytopathia, congenital vascular purpura, scurvy, vitamin P deficiency, drug or toxic purpuras.

Bleeding Time (Duke).—This test was designed to measure capillary constrictability, but it may depend on platelet and plasma factors as well. With a new Bard-Parker No. 11 blade, adjusted in a cork to a standard 4 mm., or a Hemolet, a cut is made in the cleaned fingertip. (If fingers are cold, they are first warmed in 37 C water bath for five minutes. If skin is thick, blade may be adjusted to 5-6 mm.) The middle and ring fingers are usually the most satisfactory. At 30-second intervals the blood is collected onto filter paper, without touching the cut, and time recorded with a stopwatch from cut to termination of bleeding. If bleeding continues longer than 10 minutes it may be terminated and test reported as 10+.

Bleeding Time (Ivy).—A sphygmomanometer cuff is applied and inflated to 20 mm Hg. A cut similar to that in the Duke method is made in an area of the flexor surface of the arm which appears to be free from subcutaneous veins. Blood drops are collected in the same manner. Using an ear lobe for a bleeding time has in some subjects, particularly with hemophilia, led to prolonged bleeding which has been difficult to control.

Normal range: One to six minutes.

Abnormal: The value is abnormal in thrombocytopenia, thrombocytopathia, and pseudohemophilia and rarely in hemophilia and other purely plasma factor deficiencies.

Platelet Count.—Freshly filtered diluting fluid (Rees and Ecker solution or 0.1 M sodium citrate) is drawn to the 0.5 mark in a red-cell pipette and blood (decalcified or capillary) is drawn to the 1.0 mark. Diluting fluid is again drawn to the 101 mark and the diluted blood thoroughly mixed and placed in the counting chamber. After 10 minutes, during which time the preparation is protected from drying, platelets are counted under high dry (bright light or phase) in the entire finely ruled area. The result multiplied by 2000 gives platelet number per cubic millimeter. Blank count on diluting fluid is subtracted. Results should compare with indirect count made on good ordinary Wright stain smear: Count platelets and RBC in sufficient fields to bring RBC to 1000.

* Dr. Oscar Ratnoff made it possible for us to see this patient.

Multiply platelet number counted by known RBC count divided by 1000. Also note appearance of platelets.

Normal range: 150,000 to 450,000. Low in thrombocytopenia, high in thrombocythemia.

Collection of Blood Samples.—Following neat venipuncture, 15 ml. blood is obtained in siliconed Syringe 1. This syringe is then exchanged for siliconed Syringe 2 and an additional 20 ml. collected. Blood from the first syringe is distributed (*a*) 9 ml. into 1 ml. 0.1 M sodium oxalate and (*b*) 5 ml. into a siliconed bottle containing 8 mg. dry edathamil calcium-disodium (Sequestrene) (Alrose Chemical Co.). Blood from the second syringe is distributed (*c*) 9 ml. into siliconed tube containing 1 ml. 0.1 M sodium citrate, (*d*) 2 ml. into each of two new glass 13×100 mm. tubes (start a stop watch), (*e*) 2 ml. into a siliconed 13×100 mm. tube. Tubes (*d*), (*e*), and (*f*) are 13×100 mm. tube, and (*f*) 4.5 ml. into new glass tubes mixed and chilled. Tube (*a*) is centrifuged immediately placed in a 37 C bath, and the other 10 minutes at 3000 rpm and the plasma saved cold for assay of plasma factors. Blood bottle (*b*) is used for platelet count, smear for frequency and morphology of platelets, other blood cell counts, and hematocrit, and after centrifugation the plasma is used for fibrinogen assay. Tube (*c*) is used for preparation of platelet suspension. It is first centrifuged 10 minutes at 800 rpm (cold). (Exact speed and duration of centrifugation, which allows, in a single procedure, separation of approximately 3 ml. plasma containing only a very rare RBC or WBC but most of the platelets, must be determined for each centrifuge.) The supernatant platelet-rich plasma is removed, the volume is recorded, and it is recentrifuged (multispeed) at 20,000 rpm for 45 minutes. Platelet-poor plasma is removed and reserved cold. The sedimented platelets are washed six times in 0.85% sodium chloride containing 0.2% Triton WR-1339 (an alkylaryl polyether alcohol, Rohm & Haas) and finally smoothly suspended in a volume of saline equal to 1/10 the original platelet-rich plasma volume.

Whole Blood Clotting Time.—After three minutes at 37 C the first tube (*d*) is gently tilted every 30 seconds until it can be inverted; then the second tube is treated in the same fashion, and at the time it can be inverted the glass clotting time is recorded. Tube (*e*) is observed at two- to three-minute intervals, and when it can be inverted the silicone clotting time is recorded.

Normal Range: Glass, 5-13 minutes; silicone, 22-50 minutes.

Clot retraction: This may simply be recorded as 0 to ++++, at 1 and 24 hours after clotting.

Clot Lysis: If the blood is observed to clot and within 24 hours the clot to dissolve completely, the presence of whole-blood clot lysis is recorded.

Prothrombin Consumption.—Tube (*f*) is allowed to remain undisturbed at 37 C for 1 hour from venepuncture; 0.5 ml. 0.1 M sodium oxalate is then mixed in, the clot reamed with an applicator stick, the tube centrifuged for 10 minutes at 3000 rpm, and the serum obtained. Prothrombin consumption is calculated after prothrombin has been assayed in both the plasma and this serum.

$$\text{ProT. cons.} = \frac{(\text{plasma ProT.} - \text{serum ProT.}) \times 100}{\text{plasma ProT.}}$$

Normal range: Greater than 90%.

Prothrombin Time (Quick Test).—Clotting time in duplicate at 37 C of 0.2 ml. calcium thromboplastin plus 0.1 ml. oxalated plasma.

Normal range: The exact clotting time is dependent upon thromboplastin employed; the usual normal range is 12 to 17 seconds. Clotting times are converted to per cent normal by reference to standard curves prepared for each thromboplastin, employing dilutions (with $BaSO_4$ plasma) of pooled normal plasma.

Prothrombin Assay.—Method I: Duplicate determination of clotting times at 37 C after addition of 0.2 ml. calcium thromboplastin to a mixture of 0.1 ml. of 1:10 buffered saline dilution of oxalated plasma plus 0.1 ml. of prothrombin substrate.

Method II: Ware and Seegers' two-stage method[19] modified in hypoproconvertinemic specimens[20] by addition of 0.1 ml. 1:10 diluted proconvertin to the diluting fluid.

Method III: $BaSO_4$ eluate is prepared from patient's plasma or serum in the same fashion as the standard eluate and 0.1 ml. added to an incubation mixture containing 0.1 ml. accelerin diluted 1:8, 0.1 ml. thromboplastin, 0.1 ml. proconvertin, 0.5 ml. imidazole buffer, and 3.6 ml. saline. At zero time, 0.5 ml. of 0.15 M $CaCl_2$ is added and activation allowed to proceed for five minutes to a stable clotting time, obtained in triplicate by adding 0.2 ml. of the mixture to 0.2 ml. fibrinogen. Observed clotting times are converted to units by reference to a standard curve prepared by completely activating, in a similar fashion, 0.2 ml. normal $BaSO_4$ eluate and obtaining clotting times of precise dilutions. Empirically, a clotting time of 15 seconds represents 100 units of thrombin.

Proconvertin Assay.—Duplicate determination of clotting time at 37 C after addition of 0.2 ml. calcium thromboplastin to a mixture of 0.1 ml. of 1:10 buffered saline dilution of oxalated plasma plus 0.1 ml. proconvertin substrate. Not more than 15 seconds should elapse from time of preparing dilution to time of adding calcium thromboplastin, for after this the times begin to become longer.

Proaccelerin Assay.—Method I: Duplicate determination of clotting time at 37 C after addition of 0.2 ml. calcium thromboplastin to a mixture of 0.1 ml. of 1:10 buffered saline dilution of oxalated plasma plus 0.1 ml. proaccelerin substrate.

Method II: Two-stage assay similar to prothrombin Method III, employing 0.1 ml. of standard $BaSO_4$ eluate and substituting 0.1 ml. 1:10 saline dilution of fresh $BaSO_4$ plasma for accelerin.

AHF, PTC, and Hageman Factor Assay.—Use new glass 12×75 mm. tubes; 0.2 ml. standard AHF, PTC, or Hageman-factor-deficient plasma, plus 0.05 ml. (1) 1:10 normal fresh or standard plasma (or dilutions thereof) or (2) 1:10 patient's plasma (or dilutions or concentrations thereof) or (3) 1:10 AHF or PTC or Hageman-factor-deficient plasma, plus 0.2 ml. 0.025 M $CaCl_2$. Mix, place at 37 C. Note clotting time. One hour after adding $CaCl_2$ add 0.05 ml. 0.1 M sodium oxalate and wind out clot. Measure residual prothrombin by Method I, employing 1:5 dilution rather than usual 1:10 dilution.

Conversion of Observed Clotting Time to Percentage Normal.—Reference curves employing precise dilutions of normal plasma are prepared for each assay. Daily reagent variation is controlled by testing a standard normal subject together with the patients. The normal range for the various plasma factors is approximately 60% to 140%.

Fibrinogen.—0.5 ml. plasma is placed in each of two 12×75 mm. cuvettes, and 1 ml. buffered saline is added to each. One tube is heated for 10 minutes at 56 C. Turbidometric differences are read on a Coleman Junior Spectrophotometer set at 500λ. If marked lipemia, bilirubinemia, or hemolysis is present this method may be inaccurate. A curve relating turbidity to fibrinogen concentration was first prepared and allows direct conversion of measured turbidity to percent fibrinogen.

Normal range: 65%-135%.

Platelet Thromboplastin.—Place the following in new glass 12×75 mm. tube: 0.2 ml. normal platelet-poor plasma, plus 0.05 ml. (1) 1:50 saline dilution normal platelets (or dilutions thereof) or (2) 1:50 saline dilution patient's platelets (or concentrations thereof) or (3) saline, plus 0.2 ml. 0.025 M $CaCl_2$. Mix gently, place at 37 C, record clotting time, and determine one-hour residual prothrombin after oxalating as in AHF assay. Tube (1) should contain less than 5% residual prothrombin; (3), more than 80%. Prepare additional dilutions of (1) or concentrations of (2) until a match is obtained.

Platelet Accelerator.—The procedure employed in proaccelerin Method II is modified by substituting 0.1 ml. platelet suspension (full strength) for the 1:10 $BaSO_4$ plasma. Per cent activity is obtained by comparison to dilutions of normal platelets.

Platelet Retractor.—In patients who do not show normal whole-blood-clot retraction, tubes similar to those used in the platelet thromboplastin assay, substituting full-strength platelets, are allowed to stand at 37 C for 24 hours and degree of retraction is compared with the normal.

Platelet Agglutinins.—0.2 ml. $BaSO_4$ (100 mg. per milliliter) treated serum from tube (*f*) is mixed with 0.2 ml. normal platelet suspension (diluted 1:10) and allowed to stand two hours at room temperature and overnight at 4 C. Gross appearance is noted at two hours and gross and microscopic appearance the next morning. Tube containing patient's serum is compared with normal serum and with saline for agglutination and platelet count.

Thromboplastin Generation Test (Modified from Biggs[23]).—0.2 ml. $BaSO_4$-treated plasma (diluted 1:5) plus 0.2 ml. serum (dilated 1:10) plus 0.2 ml. platelet suspension (diluted 1:10) plus 0.2 ml. 0.025 M $CaCl_2$ (start stop watch). At one-minute intervals 0.1 ml. of the mixture is added simultaneously with 0.1 ml. 0.025 M $CaCl_2$ to 0.1 ml. normal platelet-poor citrated plasma and the clotting time recorded. All procedures are carried out at 37 C. This test may be used as a screening test for detection of deficiencies in platelet thromboplastic factor, AHF, PTC, PTA, proaccelerin, and proconvertin (Stuart type) or the presence of inhibitors, by comparing the rate at which "thromboplastic activity" develops and the final clotting time (usually 10 seconds) in mixtures of normal components with patient's components. If the mixture, using all three components from the patient, results in a diminished thromboplastin generation (time longer than normal), additional tests, each substituting one normal component, give clues as to the patient abnormality. Thus, if substitution of normal platelets restores thromboplastin generation to normal, the patient suffers from either thrombocytopenia or thrombocytopathia. If substitution of normal $BaSO_4$ plasma restores thromboplastin generation, the patient is deficient in either AHF or proaccelerin. If substitution of normal serum restores the test, the patient is deficient in PTC or proconvertin (Stuart type). When either $BaSO_4$ plasma or serum are effective, deficiency of PTA or Hageman factor may be suspected. When nothing improves the thromboplastin generation, the presence of an inhibitor may be suspected. This test may also be used as an assay procedure and is particularly useful for assay of platelet thromboplastin. In this case normal $BaSO_4$ plasma and serum are mixed with the patient's platelets and the results compared to those obtained with various dilutions of normal platelets. Likewise it may be employed for assay of AHF ($BaSO_4$ plasma) or PTC (serum) if the patient's proaccelerin or proconvertin levels, respectively, are normal.

Plasma-Thrombin Clotting Time.—0.1 ml. thrombin (prepared so that 0.1 ml. will clot 0.1 ml. normal plasma in 15±2 seconds) is added to 0.1

TABLE 8.—*Preparation for Test for Circulating Anticoagulant*

	Tube No.						
Oxalated Plasma	1	2	3	4	5	6	7
Normal, ml.	0.25	0.20	0.15	0.10	0.05	0.05 (1:10)	0
Patient's ml.	0	0.05	0.10	0.15	0.2	0.2	0.25

ml. patient's plasma and the clotting time compared to that of normal plasma. Prolongation suggests hypofibrinogenemia, hyperantithrombinemia, or lack of a factor associated with the thrombin-fibrinogen reaction.

Serum Antithrombin.—$BaSO_4$ serum (as for platelet agglutinins) is heated to 56 C for three minutes and centrifuged and 1.0 ml. mixed with 1.0 ml. thrombin. At one-minute intervals, for five minutes, 0.2 ml. of the mixture is added to 0.2 ml. fibrinogen and the clotting time recorded. Initial thrombin concentration is adjusted so that when saline is substituted for serum the clotting time is 15±2 seconds. Rate of thrombin inactivation is compared to a normal. Rapid inactivation is seen in hyperantithrombinemia.

Plasma Antitissue Thromboplastin.—0.1 ml. human brain thromboplastin is substituted for ordinary thromboplastin in "prothrombin time" (Quick test). In presence of this inhibitor, comparison with a normal plasma shows a much longer time for the human brain than the ordinary thromboplastin test.

Circulating Anticoagulant: New 12×75 mm. glass tubes are prepared to contain amounts shown in Table 8. 0.2 ml. 0.025 M $CaCl_2$ is added to each tube; tubes mixed and placed at 37 C, clotting time is recorded, and one-hour residual prothrombin is determined (as for AHF assay). In the absence of anticoagulant, essentially the same clotting times and less than 10% residual prothrombin will be found in all tubes except Tube 7. In the presence of anticoagulant, the amount of residual prothrombin and clotting time will increase from Tubes 2 to 7. If Tube 2 is abnormal, dilutions of patient's plasma may be employed to titer amount of anticoagulant. In some instances, anticoagulant may be better demonstrated in $BaSO_4$-treated plasma or $BaSO_4$-treated aged serum. Employ Tubes 1, 2, and 3 for these. Tubes 5 and 6 also serve to predict how the patient's coagulation mechanism will respond to transfusion.

Anti-AHF and Anti-PTC Titers".—Incubate 0.1 ml. patient's oxalated plasma or oxalated saline with 0.1 ml. 1:5 dilution of normal plasma for 30 minutes at 29 C. Perform AHF or PTC titer on 0.05 ml. of mixture. In presence of anti-AHF or anti-PTC, patient's plasma will destroy or markedly lower AHF or PTC titer of the normal plasma. In absence of these, AHF or PTC titer will be normal.

Protamine Titration (Demonstrates Presence of Circulating Heparin-like Substances).—To 0.2 ml. plasma add 0.05 ml. of protamine (0.1%, 0.075%, 0.05%, 0.025%, 0.01%, 0.0075%, 0.005%) or 0.05 ml. saline; recalcify with 0.2 ml. 0.025 M $CaCl_2$, record clotting time and residual prothrombin as for AHF assay. Decrease in clotting time and residual prothrombin in presence of protamine suggests hyperheparinemia.

Department of Medicine, University of Pittsburgh School of Medicine (13).

REFERENCES

1. Lewis, J. H.; Tagnon, H. J.; Davidson, C. S.; Minot, G. R., and Taylor, F. H. L.: The Relation of Certain Fractions of the Plasma Globulins to the Coagulation Defect in Hemophilia, Blood 1:166-172 (March) 1946.

2. Brinkhous, K. M.: Clotting Defect in Hemophilia: Deficiency in a Plasma Factor Required for Platelet Utilization, Proc. Soc. Exper. Biol. & Med. 66:117-120 (Oct.) 1947.

3. Quick, A. J.: Studies on the Enigma of the Hemostatic Dysfunction of Hemophilia, Am. J. M. Sc. 214:272-280 (Sept.) 1947.

4. Aggeler, P. M.; White, S. G.; Glendening, M. B.; Page, E. W.; Leake, T. B., and Bates, G.: Plasma Thromboplastin Component (PTC) Deficiency: A New Disease Resembling Hemophilia, Proc. Soc. Exper. Biol. & Med. 79:692-694 (April) 1952.

5. Lewis, J. H., and Ferguson, J. H.: Hemorrhagic Diathesis Due to PTC (Plasma Thromboplastin Component) Deficiency, Proc. Soc. Exper. Biol. & Med. 82:445-448 (March) 1953.

6. Biggs, R. G.; Douglas, A. S.; Macfarlane, R. G.; Dacie, J. V.; Pitney, W. R.; Merskey, C., and O'Brien, J. R.: Christmas Disease: A Condition Previously Mistaken for Haemophilia, Brit. M. J. 2:1378-1382 (Dec. 27) 1952.

7. Rosenthal, R. L.; Dreskin, O. H., and Rosenthal, N.: New Hemophilia-like Disease Caused by Deficiency of a Third Plasma Thromboplastin Factor, Proc. Soc. Exper. Biol. & Med. 82:171-174 (Jan.) 1953.

8. Spaet, T. H.; Aggeler, P. M., and Kinsell, B. G.: A Possible Fourth Plasma Thromboplastin Component, J. Clin. Invest. 33:1095-1102 (Aug.) 1954.

9. Ratnoff, O. D., and Colopy, J. E.: A Familial Hemorrhagic Trait Associated with a Deficiency of a Clot-Promoting Fraction of Plasma, J. Clin. Invest. 34:602-613 (April) 1955.

9a. Seegers, W. H. and Alkjaersig, N.: The Preparation of Prothrombin Derivatives and an Indication of Their Properties. Arch. Biochem. and Biophysics 61:1-19 (March) 1956.

10. Owren, P. A.: Prothrombin and Accessory Factors: Clinical Significance Am. J. Med. 14: 201-215 (Feb.) 1953.

11. Alexander, B.; Goldstein, R.; Landwehr, G., and Cook, C. D.: Congenital SPCA Deficiency: A Hitherto Unrecognized Coagulation Defect with Hemorrhage Rectified by Serum and Serum Fractions, J. Clin. Invest. 30:596-608 (June) 1951.

12. Owren, P. A.: Parahæmophilia: Hemorrhagic Diathesis Due to Absence of a Previously Unknown Clotting Factor, Lancet 1:446-448 (April 5) 1947.

13. Ware, A. G., and Seegers, W. H.: Plasma Accelerator Globulin: Partial Purification, Quantitative Determination, and Properties, J. Biol. Chem. 172:699-705 (Feb.) 1948.

14. Quick, A. J., and Stefanini, M.: The Concentration of the Labile Factor of the Prothrombin Complex in Human, Dog, and Rabbit Blood: Its Significance in the Determination of Prothrombin Activity, J. Lab. & Clin. Med. 33:819-826 (July) 1948.

15. Koller, F.: Symposium: What is Hemophilia? Is Hemophilia a Nosologic Entity? Blood 9:286-290 (March) 1954.

16. Lewis, J. H.; Fresh, J. W., and Ferguson, J. H.: Congenital Hypoproconvertinemia, Proc. Soc. Exper. Biol. & Med. 84:651-654 (Dec.) 1953.

17. Hougie, C., and Graham, J. B.: The Blood Clotting Role and Mode of Inheritance of the Stuart Factor: A New Clotting Factor Distinct from SPCA, Proceedings of the 6th Congress of the International Society for Blood Transfusion, Boston, September, 1956, pp. 80-81.

18. Klein, E.; Farber, S.; Djerassi, I., and Arnold, P.: Hemostasis Following the Administration of Lyophilized Platelet Material in Secondary Thrombocytopenia, Proceedings of the 6th Congress of the International Society of Hematology, Boston, August, 1956, p. 339.

19. Ware, A. G., and Seegers, W. H.: Two-Stage Procedure for the Quantitative Determination of Prothrombin Concentration, Am. J. Clin. Path. 19:471-482 (May) 1949.

20. Ferguson, J. H.; Lewis, J. H., and Fresh, J. W.: The 2-Stage "Prothrombin" Assay in Study of Bleeding and Clotting Disorders, Yale J. Biol. & Med. 28:253-264 (Dec.-Feb.) 1955-1956.

21. Biggs, R., and Douglas, A. S.: The Thromboplastin Generation Test, J. Clin. Path. 6:23-29 (Feb.) 1953.

22. Lewis, J. H.; Ferguson, J. H., and Arends, T.: Hemorrhagic Disease with Circulating Inhibitors of Blood Clotting: Anti-AHF and Anti-PTC in 8 Cases, Blood 11:846-855 (Sept.) 1956.

Books

EDITED BY WILLIAM B. BEAN, M.D.*

An Essay on Population. Vols. I and II. By T. R. Malthus. Price, not given. Pp. 315. Everyman's Library, E. P. Dutton & Co., Inc., 300 Fourth Ave., New York 10; S. M. Dent & Sons, Ltd., Aldine House, 10-13 Bedford St., Strand, London W. C. 2, 1952.

The Value of a Human Being. By M. H. Mothersill, M.D. Price, not given. Pp. 117. Privately printed in Indianapolis, 1955.

Patterns of Survival: An Anatomy of Life. By John Hodgdon Bradley. Price, $2.25. Pp. 223. The Macmillan Company, 60 Fifth Ave., New York 11, 1938.

The Challenge of Man's Future. By Harrison Brown. Price, $1.25. Pp. 290, with illustrations. Viking Press, 625 Madison Ave., New York 22, 1956.

Darwin and Malthus ended the complacency of all thoughtful men when they showed that the earth is too tiny to give food and room to all living creatures. Philosophers since their day have realized that living implies eating, and in a pecking order with certain sinister aspects. Eat until eaten rather than eat or be eaten. There is naturally no guarantee that shrinking the world's population would change the law of the jungle, but there would be jungle enough to go around. In short, while Malthus' remedy, population restriction, would not bring us to Utopia, the opposite process, unlimited expansion of the population, insures trouble and invites disaster. And disaster will prove fatal to our way of life, if not to life itself.

"Has man a future?" This question can be answered favorably only if there is an affirmative answer to the question, "Has the intellect a function?" Modern man is the only creature who disobeys the laws of natural selection by virtue of ethical and moral beliefs and practices. We have no right way of getting rid of the congenitally weak, the habitually antisocial, and those destructive of themselves in the community. Man in short is the only species that promotes its own destruction by preserving "the lame and the halt and the blind in the rain and the cold." Physicians aid and abet the process, and who of us is wise in ways to change it. But man is at war with himself from wonderfully mixed motives, those of sentimentality and those of greed. As physicians we should think of these things.

In an epoch when the diluting effect of mass education, free for all, has resulted in a suspicion of scholarship, of excellence, and of the mind, a small residue of thoughtful persons are keenly aware that an antithinking, anti-intellectual posture has given support to a major political party and has been preached by a major news journal in this country. The term "egghead," a pleasantly original one, must apply to anyone caught reading this review. But rejecting the use of the mind is neither the exclusive property of political partisans nor new phenomenona on the face of earth. Nor indeed is thinking. Let us then for a moment fasten our attention on some eternal and perhaps insoluble problems which beset us most closely today. They are not new and they are probably coeval with man and perhaps coterminous. I am thinking of such fundamental ones as man's basic physical needs in simple terms of supply and demand. After reading Harrison Brown's most searching and disturbing "The Challenge of Man's Future" and Mothersill's "The Value of a Human Being," a much slighter book, I was led back to read Parson Malthus' "An Essay on Population." These books make useful reading for those optimists who think that technological man in every place and nation can find food, clothing, housing, and some use for leisure. Of course there will be enough for everyone, no matter how enormous that everyone may be. It takes the ability to look the world straight in the face without being overwhelmed by pessimism to endure Harrison Brown's book, with its frightening but realistic view of the future. Reduced to the very simplest form, the question he attacks is where the breaking point will come in the demand for energy and space; the supply in this case being the vastly proliferating members of the

* Communications to this Department may be sent directly to Dr. William B. Bean, State University of Iowa, Iowa City, or to the Chief Editor for transmittal to him.

human race. Few people have had the temerity or perhaps the toughness to tackle head-on our frenzied, furious, lemming-like procreative activity which causes populations to increase at an exponential rate. In spite of the fact that technological revolutions have outmoded the timing in the dire predictions of Malthus, the fact is that energy materials, foodstuffs and oils, and coal and radioactive matter, though the end of the rich stores may be far away, still are finite. Reserves are being exhausted, and the stores can be replenished very slowly, if at all. Brown's warning is that once upset it will not be possible to start a new industrial civilization all over again.

People in the United States, with their prodigality, born of luxury in the lush plenty of vast natural resources, have not realized how close to the margin some of the reserves are right now. We mine our top soil and our petroleum and destroy forests and other natural resources with wild abandon. All effort at conservation has not reversed the trend of waste. Harrison Brown's book is a detailed, thoughtful, and searching essay which expresses the realistic view that while the ultimate survival of man is not impossible, omitting some universally suicidal atomic war, there is nothing in man's history up to now which makes it probable he will find a solution for the disparity between supply and demand of energy materials. Since reserves are finite and are not automatically self-replenishing, a solution can come only by reducing the increasing birth rate. Since science now makes to every one the present of half a lifetime of extra years, we have lost or reduced the effectiveness of many of Malthus' checks on population. The check which war itself provided with the outriding Four Horsemen of the Apocalypse may now not be so much a check as finis, putting man entirely out of business or ruining half the world.

Mothersill's little privately printed book almost loses its value by hiding it in a series of formulae which seem designed to confuse the medical man in the street rather than point out the proper direction by sign posts. It is an example of medical philosophers with their sad habit of getting so enveloped in their own concepts that they tend to repel others who might enjoy and indeed profit by understanding their thoughts. Toward the end of the book things come back into focus, and the main thesis is one which would please Malthus. It is that the value of individual human beings has a reciprocal relationship to the total number. We are fast arriving at a state with far too many people for optimal living; perhaps even for survival. Mothersill has a very precise formula to recommend—birth control universally applied, for a long time limiting the number of children per family to one and then slowly raising the number but only when the world is back in what he believes the proper equilibrium, with a total of somewhere around six or seven hundred million people. His emphasis on the fact that the world over there is a fair relationship between ignorance and large families illustrates the great unlikelihood of solving this problem on an intellectual basis alone. Still, it is not impossible and is the last best hope. The most advanced and sensible people will continue to limit their population, while hordes multiply and overflow into what has always been war and devastation.

Bradley's "Patterns of Survival" was written twenty years ago, the chapters appearing as articles in various journals. The searching questions proposed by this brilliant writer and thinker, with his fine tracery and embroidery of words, are deep. He almost beguiles the reader into missing the momentous implications of his thoughts. Here is a bold and honest look at the biological nature of man. His vicissitudes, as we have record of them in evolutionary failures and successes, are to be read in the flinty records of geology and the fossil graveyards of ancient life. The emphasis again and again highlights man's potential as a thinking creature who might take an active hand in writing some of the story now and in the future by employing some of his mental equipment. Some of the optimistic view in Bradley's book results from the fact that it was written before World War II. Then there seemed to be more hope that man could live at peace with his brothers and nations could fine some ground for harmony in their schizoid and paranoid international behavior. Though the hope may still exist, Harrison Brown points out that no honest and thoughtful man should permit it to blind him to the grisly realities of the day.

Reading Malthus may be a little tedious, particularly because of the repetition of illustrative examples, reminding one a little of the eight volumes of Frazer's "Golden Bough." The vast weight of erudition and the deployment of armies of data tend to smother our attention in the luxuriant mass of detail. Though Malthus' timetable was off, we now realize the truth of his basic proposition—that the relation between man's procreative capacity and the development of self-perpetuating supplies of food and energy were always overbalanced by an expanding population. With instinctual drives given a freer play by a more dynamic health, with war

changed from a check on population to a possible mechanism of complete destruction, we have as the one faint hope the harnessing of man's intellect. This, indeed, is the only thing which keeps the bleak and frigid evils of the day from annealing us in the frozen posture of despair. For mankind in ancient days has overcome what seemed hopeless odds in the face of ever-encroaching vicissitudes. We should not be unmindful of the fact that the evolutionary past is strewn with the graveyards of the last survivors of many species whose history we can quarry from the fossil record. The simple lesson is that the price of failure on a global scale is extinction, and unsentimental nature may turn her busy hands to other matters. Man's history on earth will be but a fleeting glimpse of a dim light burning in an empty room.

WILLIAM B. BEAN, M.D.

Notes on Atomic Energy for Medical Officers. By The Royal Naval Medical School. Price, $4.75. Pp. 169. Philosophical Library, Inc., 15 E. 40th St., New York 16, 1956.

This book has been prepared for those physicians whose training and experience has not given them an understanding of atomic energy and the effects of radiation on the living organism. Its purpose is to provide the basic knowledge a medical officer or other physician needs to understand the effects of an atomic explosion and the dangers of other types of radiologic warfare. Emphasis is placed on scientific background. Explanations of the phenomena involved are simple and thorough, and, because of this, the purpose of the book is achieved.

The first chapter deals with introductory physics, and subsequent chapters, with x-rays, atomic structure, natural radioactivity, transmutation of elements, artificial radioactivity, and ionization. With this background well established, the book progresses to consideration of the release of atomic energy and the properties of fission products. This is followed in turn by a discussion of the sequence of events in the explosion of an atomic bomb and the results of the release of radioactivity and thermal and mechanical energy.

At this point there is a return to basic scientific facts concerning the individual cell and the effects of radiation upon it. In the next chapter the effects of radiation on the whole body are presented. The last four chapters deal with the estimation of military hazards, the treatment of radiation casualties, monitoring instruments, and protection against radiation.

In addition, there are seven appendices, of which the first five are tables and the last two, short discussions of the uses of isotopes and of the hydrogen bomb. There are also a bibliography for those who may wish to pursue the subject farther and a glossary which most physicians will find very useful.

This book is to be recommended to the many physicians who find themselves involved in one of the ramifications of atomic energy and particularly to those concerned with civil defense.

ROBERT C. HARDING, M.D.

Vitamins and Hormones: Advances in Research and Applications. Vol. 13. Edited by Robert S. Harris, G. F. Marrian, and Kenneth V. Thimann. Price, $9. Pp. 382, with illustrations. Academic Press, Inc., 111 Fifth Ave., New York 3, 1955.

I have gotten somewhat behind in my reading of this series of annual volumes. They are extremely helpful to those interested in clinical nutrition and endocrinology, as well as the investigators in these fields for whom the volumes are primarily intended. This particular number, Volume 13, has a great many monographs which should be of concern to all people practicing clinical medicine. The monographs are critical and selective. They do not try to give every reference, nor are the writers content merely to copy statements or a list of facts, but they give interpretations. One aspect of the relationship of nutrition and infection is dealt with by Axelrod and Pruzansky, in discussing the role of vitamins in antibody production, a field with much speculation; but despite a great deal of work which has been done, knowledge is not yet well advanced. Deuel and Reiser present a clear picture of the physiology and biochemistry of the essential fatty acids. This topic has come in for breathless publicity recently. Those who wish to get a thoughtful background for much of the current speculation can find no better source than this monograph. Mapson's essay on the biosynthesis of ascorbic acid and the essay of Ford and Hunter on the role of vitamin B in metabolism of microorganisms are less practical, but they give good background material in the field of nutrition and vitamins. An extremely searching and comprehensive review of the chemotherapeutic action of vitamin B_{12}, by Ungley, should help clarify this mysterious problem, the complexities of which certainly have not been resolved by the identification and synthesis of vitamin B_{12}.

Ungley has made notable contributions to this field. Current concepts are admirably expounded, and much of the complexity is removed from chaos and put into a definite form of organization. Vitamin requirements of human beings are dealt with by Pett in a way which certainly will make the fabricators of tables of allowances uneasy. This is a searching and scholarly article which should be required reading for everyone who feels called upon to prescribe vitamin capsules and tablets. Smith reminds us of the relatively scanty evidence on which our concepts of the relationship of infection and nutrition are based. Bullough analyzes the problem of hormones and mitotic activity. Perhaps the most challenging and fascinating of all the essays is Hechter's scholarly discourse on possible mechanisms of hormone action. To those who are self-satisfied about advances in our understanding of the clinical use of hormones it will be shocking to find out how small is our supply of hard-won knowledge and how slim the evidence for many of the accepted formulations and generalizations regarding hormone action.

These are particularly stimulating monographs which, read selectively, used for reference, or studied *in extenso*, should be well known to practicing physicians. Whereas the title of the series, "Vitamins and Hormones," probably should be "Vitamins or Hormones," since there are very few studies of the interrelationships, this series of annual volumes should be on hand at all times for reference. The British and American editors and contributors have given an example of cooperation among the scientists, physicians, and scholars who have revealed some of the state of science today. As an international effort, it exemplifies the unity of science.

WILLIAM B. BEAN, M.D.

Proceedings of the Third National Cancer Conference, Detroit, Michigan, June 4-6, 1956. Sponsored by the American Cancer Society, Inc., and National Cancer Institute, U. S. Public Health Service. Price, $9. Pp. 961, with numerous illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; 2083 Guy St., Montreal, 1957.

The Third National Cancer Conference was held June 4-6, 1956, under the joint sponsorship of the American Cancer Society, Inc., and the National Cancer Institute, U. S. Public Health Service. An intensive program had been arranged on clinical, basic, and applied cancer research; the purpose of the meeting was to foster communication among cancer researchers, discussions among practitioners, and cross pollination of ideas between the two groups. The discussants were from the United States, mainly, but many geographical areas were represented. The transactions of the meeting are presented in a single- well-bound volume with good format. The indexing is primarily by author, not subject material.

Six lectures were delivered by authorities on the following subjects: epidemiology as a tool in cancer research; radiation neoplasia; the virus etiology of cancer; chemical effects of growing tumors on the host with particular reference to iron; factors influencing the curability of cancer; and the measurement of morbidity. These lectures are provocative and instructive; they are well worth reading.

Symposia were conducted on cancer of the breast, prostate, lung, female genital tract, gastrointestinal tract, and head and neck; also on the chemotherapy of cancer and on lymphomas and leukemia. An additional joint panel was held on cancer of the breast and prostate. The material presented by the panelists from the latter three symposia brought the audience abreast with data largely from the experimental and statistical laboratory. The material published from the other symposia described more broadly various current therapeutic issues and results. Controversial subjects seemed to be recorded objectively. Almost uniformly each panelist listed a documentary bibliography from which further information might be drawn by the reader.

The final symposium, on end-results in the treatment of cancer, merits comment. At this symposium collected data from three central registries and ten hospital registries were presented for nineteen anatomical sites. The hope had been to present results of cancer therapy in America at midcentury. The collection of data was incomplete and possibly needed discriminatory scrutiny, but reflected, if nothing more, that the over-all results of cancer therapy in America need improvement. Comments were made by various authorities on eleven entities. These were sound presentations, although there was some individual enthusiasm when personal experience or prognostications were drawn upon. The operative mortality for esophageal carcinoma seemingly was understressed, and in prognosticating upon the survival for localized colonic cancer, a five-year survival of 90% parallels or slightly exceeds the declining actuarial curve for the American population in this age group.

I recommend this volume whole-heartedly as a valuable adjunct for medical libraries. The book should be a possession of all those interested in neoplastic diseases. The index handicaps its use as a student reference.

ROBERT C. HICKEY, M.D.

Diseases of the Heart. Ed. 2. By Charles K. Friedberg. Price, $18. Pp. 1161, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5, 1956.

Diseases of the Heart and Circulation. Ed. 2. By Paul Wood. Price, $15. Pp. 1005, with illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5, 1956.

Very remarkable revisions have been made in the second editions of these two textbooks of cardiology. To compare each with its earlier edition indicates graphically the truly fabulous strides which have been made in cardiology during the decade since the end of World War II. They both reflect admirably the forces converging often from independent and most unlikely sources which have revolutionized cardiology. It cannot be said that any one of them is more important than another. They include (1) more orderly comprehension of the hemodynamics of the circulation, based to a large extent on information obtained from cardiac catheterization studies; (2) the surgical invasion of the heart, which now is the accepted arena of procedures which reconstruct, repair, and even cure a host of congenital and acquired lesions; (3) the development of effective pharmacologic agents to lower the blood pressure in hypertension; (4) antibiotics with their frequently curative role in syphilis and bacterial endocarditis and their preventive virtue in rheumatic fever; (5) anticoagulants for use in thromboembolic disorders; (6) the comprehension of some of the roles of the kidneys in electrolyte and fluid metabolism and water retention; (7) definite advances in understanding certain rare diseases, such as the hyperserotoninemic syndrome of metastatic carcinoid, certain forms of dissecting aneurysm, intracardiac tumors, Marfan's syndrome, and many other conditions; (8) the use of the many leads of the electrocardiograph to map the no longer hidden secrets of the heart, and (9) angiocardiovenography. It is too early yet to say whether the first crack of light indicates that a breakthrough on arteriosclerosis is at hand or another flash in the pan.

For anyone with clinical orientations, these advances must have great practical importance. The clinician once again is assuming the dominant role. He must determine by a comprehensive study of the patient, the significance of his symptoms, the diagnosis and interpretation of his signs, and the meaning of his murmurs, unless he is bemused by all the machines and gadgets. No longer is the realm of congenital heart disease an outlandish area off the reservation, a territory for harmless crackpots who make a fetish of clinical perfectionism.

Friedberg's book starts right off with graphic methods of cardiac examination, and only in the second section, dealing with cardiac failure, does he discuss signs, symptoms, and the clinical history. After the cardiac arrhythmias come diseases of the coronary arteries and coronary heart disease, then structural abnormalities of the heart, an analysis of the etiologic forms of heart disease, and special problems in heart disease. Wood manages to get more into a compressed space than Friedberg, who in turn has more detail. I did not fail to find some reference to anything I looked up, including serotonin, in both books. Wood has a dry style shorn of all possible ornament or redundancy, which holds true even when he is discussing the almost interminable laboratory procedures which have become essential in cardiology. Friedberg's book tends at times to contain so much material that it becomes a little turgid. However, both books are easy to understand and easy to find one's way around in. Friedberg has much more emphasis on American medical writings, as one would expect, but there is a surprising uniformity in so many areas covered in both books that we may conclude that most diagnostic, therapeutic, and prognostic elements already have become standard, if not standardized. When we recall the long struggle of the electrocardiographers to achieve a rational use of their machines, the speed of change in the last few years is dramatic. The quiet revolution brought about by Wilson permeates both books. Those who wish to probe into the mysteries of the ballistocardiograph, vector analysis, and the newer concepts of pharmacodynamics will not be disappointed in either book.

One unfortunate omission from Friedberg's book is the titles of the articles listed in the bibliography at the end of each chapter or section. This makes the book less valuable as a source book or a work of reference. Unless one is closely conversant with all the papers referred to, failure to provide titles of articles leaves one with no better guide than his knowledge of the person who wrote the paper, if, indeed, he has that. It is as though in the classified

advertising section of the phone book the names and the phone numbers were listed at random without saying who did what, said what, or sold what.

Each time I read a section in one book, I thought the other one would disappoint me, but this never happened. The books are different in format, in organization, and in style; but both are excellent. By continuing the high performance of the first edition, they establish a standard for textbooks of cardiology. Both greatly surpass those of an earlier day and are fitting tributes to the clinical skill of their authors' experience. Their ability to digest and assimilate so large a body of material reflects the fact that they have grown up in the period of great advances and have been part of the progress. Probably newcomers on the scene will not be able to encompass so much. Thus I suspect that just as the great textbooks of medicine have passed beyond the competence of a single person, so the future textbook of cardiology will become an assemblage of monographs by those who have become especially proficient in one or another of the subspecialties of cardiology, itself a subspecialty of internal medicine. For the present, we can be glad that there are some still able to integrate the whole field as well as it is done in these two fine texts, which can be recommended heartily to internists and cardiologists. I would advise them to use both books, since I cannot choose either as superior.

WILLIAM B. BEAN, M.D.

The Importance of Overweight. By Hilde Bruch, M.D. Price, $5.95. Pp. 438. W. W. Norton & Company, Inc., 55 Fifth Ave., New York 3, 1957.

In this book the complex subject of obesity is handled in a comprehensive and sympathetic manner. The author believes that obesity is only the conspicuous reflection of an inner disease state which may originate from the interaction of cultural, psychological, and metabolic factors. Because obesity may represent the best possible adjustment which the overweight patient has been able to make to his own life situation, treatment must involve more than the curt adjunct "to stop eating and exercise more." Perhaps, as the author puts it, a portion of the problem may lie in the present standards of beauty which aim to a "near emaciation" of the human body. In other cultures the obese have been admired as symbols of prosperity and not rejected as in our own.

Although the author's orientation is basically psychiatric, she presents an excellent discussion of the history of obesity as a medical problem and reviews the current evidence regarding the metabolic causation of obesity. She does not neglect that most common form of obesity, "the creeping obesity of middle age," which may respond well to simple dietary measures. Other patients, especially those with obesity developing in childhood, require definitive psychiatric treatment, as is documented by numerous case histories.

WILLIAM E. CONNOR, M.D.

Pica: Survey of the Historical Literature as Well as Reports from the Fields of Veterinary Medicine and Anthropology, the Present Study of Pica in Young Children, and a Discussion of Its Pediatric and Psychological Implications. By Marcia Cooper. Price, $3.75. Pp. 99. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

It is indeed a pleasure to encounter a book so charmingly and informatively written as this one. Almost half of the book is devoted to a comprehensive discussion of the historical aspect of pica drawn from writings of ancient, medieval, and modern times. This section would be most intriguing to anyone interested in medical history.

The remainder of the book is concerned with an elaboration of the thesis that pica is not something of purely historical interest, but has very real application in medicine today. Dr. Cooper draws her information from a study in Baltimore of 784 cases of children over 6 months of age, of whom 21.9% had evidence of the symptom of pica. She points out that these children almost exclusively had substandard diets. The implication is made that the poor nutrition is invariably an important factor in the production of this symptom. Feeding or nutritional problems had a greater incidence among the pica group, as contrasted with the non-pica group.

Although the study is concerned with children, there is implication of the importance of this symptom in adults, especially pregnant women. This very readable book will have interest not only for pediatricians but also for psychologists, nutritionists, and internists.

ROBERT B. KUGEL, M.D.

Symposium: The Management of Tuberculosis. Edited by Irving J. Selikoff, M.D. Price, $5. Pp. 316, with numerous illustrations. Waverly Press, Inc., Baltimore, 1956.

This book consists of a number of contributions to a symposium on the management of tuberculosis and was distributed as the July-August issue of the *Journal of the Mount Sinai Hospital.* The contributors are members of the staff of the Mount Sinai Hospital, New York.

Following an outstanding chapter on the chemotherapy of tuberculosis by guest editor, Selikoff, in which is included the history of antituberculosis drug evolution, there are presented, in separate chapters, the topics of management of pulmonary tuberculosis; resection for pulmonary tuberculosis; collapse therapy; tuberculoma; tuberculosis in childhood; pleural tuberculosis with effusion; meningeal, renal, lymphatic, cutaneous, female genital, skeletal, intestinal, and laryngeal tuberculosis; diabetes and tuberculosis; tuberculosis in pregnancy; relapse and rehabilitation; pulmonary function in tuberculosis, and, finally, two case reports on long-term observation of patients treated with isoniazid when that drug was first available. Absent are discussions of several other forms of extrapulmonary tuberculosis, such as otic and male genital involvement, which might have made this symposium more complete.

The contents, in general, are very up-to-date in a field which has undergone a major evolution in the past decade, and it is fortunate that we are presented with a work of this type at a time when there appears to be somewhat of a lull in tuberculosis therapy progress.

Most of the material is presented in a clear, concise manner. In keeping with the title of the book, the authors have dwelt principally on therapy. However, enough background of diagnosis, pathology, and other pertinent aspects is given to provide an adequate total picture of each form of tuberculosis under discussion.

The chapter on cutaneous tuberculosis has the shortcoming of reporting large numbers of experiences of other authors, many from foreign countries, with older drug and treatment duration regimens at the expense of reporting current optimum treatment regimens. Perhaps such information is not available in the same degree as for other forms of tuberculosis. The chapter on intestinal tuberculosis is excellent in all respects except for the paucity of discussion of its current status as regards incidence and management in sanatorium patients.

As might be expected when several authors, from one medical center, write about one disease as its affects different organ systems, there tends to be some repetition of information steadily through the book, and certain concepts tend to be stereotyped. An example of the latter is the frequency with which triple drug therapy (streptomycin, isoniazid, and PAS) is recommended, to the virtual exclusion of dual drug therapy (isoniazid plus either PAS or streptomycin), which is so common throughout the country.

The book is not indexed, but each chapter has abundant references. It is a valuable aid to everyone who treats pulmonary tuberculosis or its extrathoracic complications.

CHARLES W. GRAY, M.D.

Personality, Stress and Tuberculosis. Edited by Phineas J. Sparer, M.D. Price, $12.50. Pp. 629, with 34 illustrations. International Universities Press, Inc., 227 W. 13th St., New York 11, 1956.

This volume contains a series of lectures presented at the Memphis Veterans' Administration Hospital in 1955 and 1956 by a number of prominent physicians and clinical psychologists. The lecture series, in the words of the editor, "constituted a coordinated teaching venture on the interrelationships of the medical and psychological sciences pertaining to tuberculosis."

Following the editor's introduction and three separate and thoughtful forwards, the thirty-three chapters are presented in four parts. The first, entitled "Basic Considerations," deals with endocrine and psychosomatic aspects of disease, in particular of tuberculosis. Parts two and three deal with clinical applications of psychological research and psychotherapy as applied to tuberculosis patients in general and to some of the special problems met with in their management, especially the one of irregular discharge. Fortunately, the patient's physician, and all hospital staff members, come in for considerable attention in several of the chapters. While hesitant to single out individual contributions in this book, I should like to mention Dr. Harry A. Wilmer's lecture on "Pity, Sympathy and Empathy," and Dr. Joan K. Jackson's discussion regarding "Skid Road" alcoholic tuberculous patients, as particularly meritorious from

the standpoints of doctor-patient relationship and of understanding and dealing with one particular segment of the tuberculous population.

Part four consists of a single chapter presenting a comprehensive psychosomatic program aimed at the hospital treating tuberculosis. It should be studied by those responsible for policy formulation in such hospitals.

Numerous references are cited after each chapter, and the whole volume is surprisingly well indexed, considering the fact that it is a compilation of works by many different authors.

This volume presents a certain amount of inconsistency of thought, to be expected with multiplicity of authorship; much discussion is based on philosophy and conjecture rather than on factual information. This is noted particularly in dissertations regarding possible relationships between personality make-up and the development of active tuberculosis, which are refuted by other authors on the basis of factual objective studies. All in all, this is a worthwhile volume for physicians and allied professional co-workers who treat patients with tuberculosis. It is also of value to psychiatrists in general.

C. W. GRAY, M.D.

News and Comment

ANNOUNCEMENTS

Discontinue Shipment of Medical Books to Korea.—The American-Korean Foundation and the United States Army Medical Service have announced the discontinuation of their joint project of shipping medical books contributed by individual physicians, medical schools, hospitals, and state and local medical societies to Korea.

Books should not be sent to the Sharpe General Depot in California as in the past, for facilities no longer exist for packing and transshipping to Korea.

In making the announcement, Howard A. Rusk, M.D., President, American-Korean Foundation said, "The response of physicians and medical groups throughout the country for our appeal for books for Korean medical schools has been so generous that further contributions are not needed." As a result of this program, Dr. Rusk stated, over 77 tons, valued at $76,000, of medical texts, references, and periodicals have been shipped to Korea for distribution to Korean medical schools.

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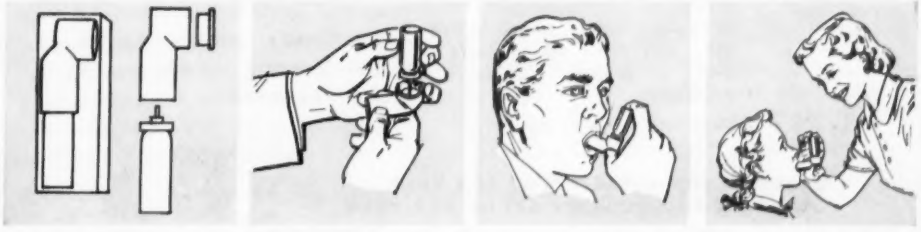

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Each METAMINE SUSTAINED tablet slowly releases 10 mg. of METAMINE, the unique, amino nitrate, to provide lasting, 12-hour protection from attacks of angina pectoris.

Simplified dosage—just 1 tablet on arising, and 1 before the evening meal.

Greater economy for your patient with angina pectoris.

Supplied: METAMINE SUSTAINED, 10 mg., bottles of 50 sustained-release tablets. Also available: METAMINE, 2 mg., in bottles of 50 and 500, and METAMINE (2 mg.) with BUTABARBITAL (¼ gr.), bottles of 50 tablets.

[1]Fuller, H. L. and Kassel, L. E.: Antibiotic Medicine and Clinical Therapy, 3:322, October 1956.

Metamine®

triethanolamine trinitrate biphosphate, LEEMING, 10 mg.

Sustained

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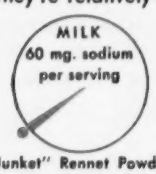
desserts for cardiac patients?

certainly!

If they're low sodium

"Junket" rennet desserts are excellent for the cardiac patient who is permitted milk, as they average about 62 mg. per ½-cup serving... of which "Junket" Rennet Powder contributes only 2.0 mg.[1] The balance of about 60 mg. sodium per serving is in the whole milk from which "Junket" rennet desserts are made. They're relatively low in caloric content too . . . 128 calories for an average ½-cup serving . . . and high in nutritional value.



●"Junket" Rennet Powder 2.0 mg. per serving

Whenever milk is permitted on the sodium restricted diet, refreshing, delicately flavored "Junket" rennet desserts may be safely advocated.

[1] Based on average of 7 flavors. Analysis of sodium content made by Foster D. Snell, Inc., New York City.

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RENNET POWDER

Makes *Fresh* Milk into Rennet Desserts

"Junket" Rennet Powder — Vanilla, Chocolate, Lemon, Orange, Raspberry, Maple, Strawberry.

"JUNKET" (Reg. U.S. Pat. Off.) is the trade-mark of Chr. Hansen's Laboratory, Inc., Little Falls, N.Y., for its rennet and other food products.

High solubility of "Thiosulfil" insures prompt bacteriostatic concentrations at site of urinary tract infections

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Brand of sulfamethizole

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Relaxes without impairing mental or physical efficiency

. . . well suited for prolonged therapy

1 **"The primary finding of these studies is that meprobamate ['Miltown'] alone . . . produces no behavioral toxicity in our subjects as measured by our tests of driving, steadiness and vision."**

Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Ann. New York Acad. Sc. 67:701, May 9, 1957.

2 **"Since it [meprobamate—'Miltown'] does not cloud consciousness or lessen intellectual capacity, it can be used . . . even by those busily occupied in intellectual work."**

Keyes, B. L.: Pennsylvania M. J. 60:177, Feb. 1957.

3 **". . . the patient never describes himself as feeling detached or 'insulated' by the drug ['Miltown']. He remains completely in control of his faculties, both mental and physical . . ."**

Sokoloff, O. J.: A.M.A. Arch. Dermat. & Syph. 74:393, Oct. 1956.

4 **"It ['Miltown'] . . . does not cloud the sensorium, and has a helpful somnifacient effect devoid of 'hangover'."**

Kessler, L. N. and Barnard, R. D.: M. Times 84:431, April 1956.

5 **"In anxiety and tension states, meprobamate relaxes without dulling cortical function to the same extent as the commonly-used barbiturates."**

Rindskopf, W., Ravreby, M., Gutenkauf, C. and Sands, S. L.: J. Iowa M. Soc. 47:57, Feb. 1957.

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Miltown®

2-methyl-2-n-propyl-1, 3-propanediol dicarbamate—U.S. Patent 2,724,720

TRANQUILIZER WITH MUSCLE-RELAXANT ACTION

SUPPLIED: *400 mg. scored tablets*
200 mg. sugar-coated tablets

USUAL DOSAGE: *One or two 400 mg. tablets t.i.d.*

Literature and samples available on request

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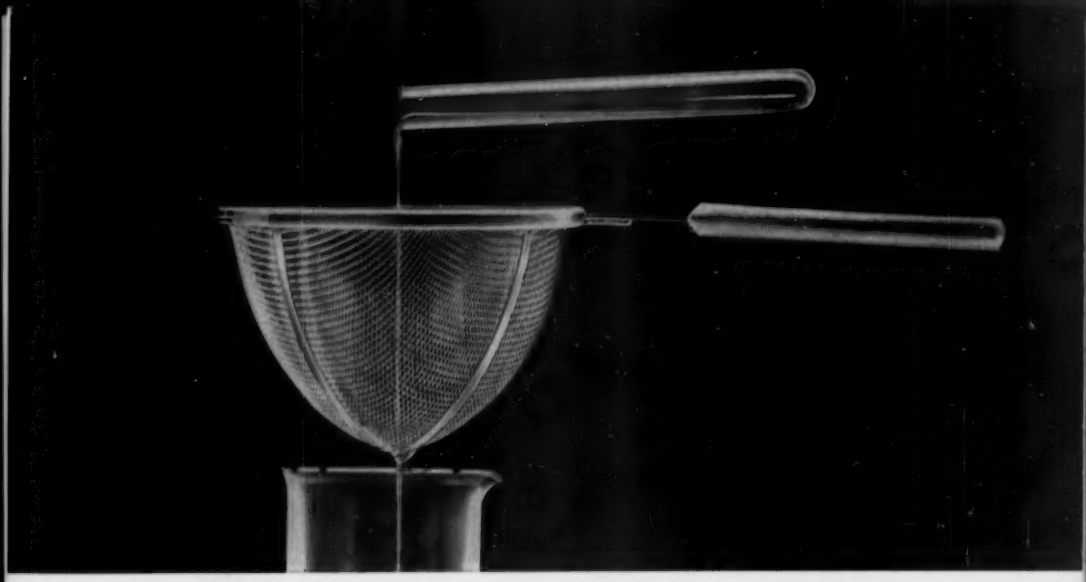

controlling suspended solids?

A uniform concentration of solids in your thromboplastin suspension is essential for accurate results. Variation in the number of particles alters the prothrombin time of patients on anticoagulant therapy.[1] Simplastin (the pre-extracted, standardized thromboplastin-calcium) is carefully controlled to contain a uniform amount of suspended solids, assuring reproducible determinations.

Many controls go into Simplastin which the average laboratory is not normally equipped to carry out. These are particularly reflected in the reproducibility of prothrombin times of patients on anticoagulant therapy, since essential clotting factors are drastically reduced in the therapeutic range (and also in dilute normal plasma).

You can demonstrate this reproducibility in your laboratory. Simply test three different vials of Simplastin with a single plasma of a patient on anticoagulant therapy (over 30 seconds). Then repeat, using the same plasma and three different ampuls or bottles of any other thromboplastin preparation. Let the results speak for themselves. We will be happy to send you three 20-determination vials without charge in order for you to make this evaluation.

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Reference: 1. Phillips, G. E., and Lenahan, J. G.: J. Lab. & Clin. Med. *46*:713 (Nov.) 1955.

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Tablets ½ gr., ¾ gr., 1½ gr., 3 gr.
Sedative dose
½ to 1½ grains
3 or 4 times daily.

Winthrop

* Smith, J. A.: *J.A.M.A.*, 152:384, May 30, 1953. Brown, W. T., and Smith, J. A.: *South. Med. Jour.*, 46:582, June, 1953. Smith, J. A.: *Postgrad. Med.*, 16:316, Oct., 1954. McClintock, W. H.: *Jour. Florida Med. Assn.*, 41:715, Mar., 1955.

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